BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 1 1951

THE ADRENAL CORTEX AND RHEUMATOID ARTHRITIS*

BY

EDWARD C. KENDALL, Ph.D.

Rochester, Minnesota

On September 21, 1948, at Rochester, Minnesota, 100 mg. of one of the hormones of the adrenal cortex designated "compound E" was injected intramuscularly into a patient who had rheumatoid arthritis. On September 28 Dr. Philip S. Hench had to depart from Rochester for London in order to deliver, on October 15, his Heberden Oration before members of this society. Those of you who heard Dr. Hench at that time may have been impressed with the vigour with which he presented the message which he brought to you, but I can assure you that his mind was troubled. On the one hand, there was reason to hope that perhaps something great had been accomplished. On the other hand, there was the disturbing thought that it might not be possible to repeat the result obtained in that single case on September 21.

So far as the patient back in Rochester was concerned everything was most satisfactory. She had been progressively disabled for five years, but after injection of the adrenal hormone for a few days all pain and stiffness had disappeared and she walked out of the hospital in a gay mood. Although this remarkable event had brought turbulence to the mind of Dr. Hench, it had nothing to do with the content of his Heberden Oration, since his manuscript had been prepared some time before the first injection of compound E was given. You will remember that Dr. Hench presented evidence which showed that rheumatoid arthritis is a reversible disease, and he suggested that some substance X, probably a constituent of the body, could bring about remission of the symptoms. If you will read the lecture (Hench, 1949) you will not find a discussion of the relationship of the adrenal cortex to rheumatoid arthritis. Indeed, what little mention of this he had made in an early draft was deleted, for neither Dr. Hench nor I wanted to make a premature announcement of what we hoped to show concerning the nature of substance X.

For many years Dr. Hench had searched for some clue that would reveal the nature of substance X (Hench, 1950). He had investigated the effect of jaundice induced by lactophenin, the influence of bile acids and their derivatives, bilirubin, lecithin, and an extract of the adrenal cortex. But the first injection of compound E, or cortisone, as it is now known, was not accidental, nor was it based on a hasty decision. During the previous ten years Dr. Hench and I frequently had discussed the nature of rheumatoid arthritis and had decided to use cortisone as soon as it became available.

The unhappy combination of events which troubled Dr. Hench when he gave the Heberden Oration in 1948 can be understood easily. The result of the injection of cortisone was too gratifying and too important to be ignored; it appeared to be the answer to years of frustration, and yet it was necessary to refrain from any mention of the treatment of a single patient before the Heberden Society. To give the Heberden Oration in 1951 is a source of great satisfaction to me, for now you know that the first patient has been followed by many thousands of others, and that the early misgivings have been replaced with assurance based on the knowledge that cortisone brings relief from the symptoms of rheumatoid arthritis, despite the fact that we do not yet know just how this is accomplished.

I wish it were possible to make a statement concerning the identity of substance X. But substance X has never been isolated as a chemical compound. It was described only in terms of its physiological activity, which was related to the physiological activity induced by both pregnancy and jaundice. Cortisone may well be substance X so far as pregnancy is concerned, but the relationship between jaundice and rheumatoid arthritis still remains obscure. Perhaps in jaundice less of X is required, but speculation alone about this matter cannot bring the answer. As more work is carried out, the influence of jaundice on rheumatoid arthritis will become evident. As we come to know more and more about cortisone the importance of the identity of substance X grows less, but the significance of the message delivered in 1948 by Dr. Hench—namely, that rheumatoid arthritis is reversible—will continue to gain importance, for ultimately this fact will be concerned with the aetiology and treatment of the disease itself.

There is another difference between the subject matter of the Heberden Oration of 1948 and that of 1951. Dr. Hench presented his results in terms of clinical experience. The chemical aspects of the problem were not mentioned in any important way. But in 1951 a discussion of the relationship of a product from the adrenal cortex to rheumatoid arthritis can be stated in the precise chemical terms of structural organic chemistry, and the daily requirement of a pure crystalline compound can be expressed in milligrams. But perhaps the greatest difference is in the attitude of the specialist

*Heberden Oration read before the Heberden Society, London, England, on September 19, 1951.

and the public towards rheumatoid arthritis. The subject, rheumatology, has come into its own. The sustained interest is based on recent advances in our knowledge of the hormones of the adrenal cortex, and it is my privilege to-day to tell you something about these new results.

Chemical Phase of the Investigation

Almost twenty years were required for the chemical phase of the investigation. During the first ten years the chemical nature of the adrenal cortex was explored. This work was carried out by Professor Reichstein and his associates in Zurich, Switzerland, and in the biochemical laboratory of the Mayo Foundation at Rochester, Minnesota, by my associates and myself. At this time I wish to express my appreciation for the essential contributions made by my associates, without whose help the investigation could not have been completed. In addition, important contributions came from the laboratory of biochemistry of Columbia University. These were made between 1933 and 1936 by Drs. Wintersteiner and Pfiffner (Reichstein and Shoppee, 1943 ; Kendall, 1950a, 1950b ; Kendall *et al.*, 1946–51).

By the year 1940 it was generally agreed that the 28 steroids that had been separated from the gland could be divided into four groups. First were certain sex hormones—androgens, oestrone, and progesterone—which were not characteristic of the adrenal cortex. Second was a group of steroids which were found only in the adrenal cortex, but which were physiologically inert. Third were six derivatives of Δ^4 pregnene, all of which possessed physiological activity. Fourth was a residue which remained after separation of the crystalline compounds. This fraction, which has been available for about fifteen years, exerts a strong effect on renal function, and indeed is essential for the control of the metabolism of electrolytes, but its chemical nature has not been established and it is still known as the "amorphous fraction."

After the six crystalline compounds had been isolated from the adrenal glands and their structure had been determined, it became apparent that before any investigation could be carried out in the field of clinical medicine some source for these hormones other than the adrenal cortex would have to be found. This was true not only because of the expense involved in the isolation of the hormones but also because the supply of adrenal glands was limited.

For this reason, attempts were made in Professor Reichstein's laboratory and in my own to devise methods by which these steroids could be prepared from some starting material other than the adrenal cortex. Professor Reichstein was the first to prepare 11-desoxycorticosterone, corticosterone, 11-dehydrocorticosterone, and 17-hydroxy-11-desoxycorticosterone (Reichstein and Shoppee, 1943). However, except for 11-desoxycorticosterone, the method which was used could not be employed for large-scale production of these compounds. A suitable procedure for large-scale production of 11-dehydrocorticosterone (compound A) was devised in my laboratory during the years 1940 to 1944, and by the end of 1946 Dr. L. H. Sarett, in the research laboratory of Merck & Co., Inc., expanded the scope of this method by the addition of one more step which resulted in hydroxylation at position 17. This afforded 17-hydroxy-11-dehydrocorticosterone, first called "compound E" and now designated "cortisone" (Sarett, 1948). In 1950 a close relative of cortisone was prepared in the research laboratories of Merck & Co., Inc. This is 17-hydroxycorticosterone, first called "compound F" and now designated "hydrocortisone" (Wendler *et al.*, 1951).

But merely to describe the preparation of these steroids from starting material derived from bile, rather than from the less abundant adrenal cortex, is an incomplete statement of the contributions of the chemist. New means to carry out some of the essential changes in the starting material have been found. The hydroxyl group at C-17 can be introduced by no fewer than four different methods, and the yield for one of the steps—introduction of the double bond in ring A—has been improved in my laboratory to such an extent that the amount of starting material originally required for the daily maintenance of 35 patients will now furnish the same amount to 93 patients (Kendall *et al.*, 1946–51).

An Outstanding Contribution to Medicine

The production of cortisone by Merck & Co., Inc., is without precedent, and the distinguished record of their contribution to medicine will be appreciated by an ever-increasing number of grateful patients. The rapid decrease in the cost of cortisone is to-day an important factor in the use of this hormone in clinical medicine. However, still further reductions in the price of cortisone will occur, since the chemist has not yet finished investigating methods for the production of this hormone. The innermost portion of the molecule, ring C, has now come within the reach of the chemist, and new sources of starting material from the plant kingdom will soon be available. Most significant advances have come from the laboratory of Professor Woodward and his associates at Harvard University and from the laboratory of Professor Sir Robert Robinson at Oxford. They recently have reported the total synthesis of the steroid nucleus, and the way is now open for the application of this knowledge to the total synthesis of cortisone (Robinson, 1951 ; Woodward *et al.*, 1951).

Organic chemists have made important contributions to another phase of the work which already has been of help to the physiologist and the clinician. This work is the preparation of 50 or more steroids, closely related to cortisone, so that it has been possible to determine the physiological significance of the various functional groups in the molecule (Polley and Mason, 1950).

Finally, still other chemists have devised methods for the determination of adrenocortical steroids in the blood and urine. These results indicate the amount and distribution of the steroids in the secretion of the adrenal cortex, the fate of cortisone after it has been administered, and some insight into the daily amount of cortisone that can be produced by the normal human adrenal cortex.

Physiological Studies

In the meantime, physiologists have studied the mechanism which controls the activity of the adrenal cortex and the various influences which affect the stimulation of the gland through the release of the adrenocorticotropic hormone of the anterior pituitary body, designated A.C.T.H. All these are recent advances, and many of them have been stimulated by the results which followed the injection of cortisone on September 21, 1948.

It is interesting to recall the circumstances which prevailed at the time of the first injection, for as we review them now it is evident that the method devised for the administration of the first dose of cortisone conformed

remarkably to the conditions which we now know are essential. In short, it was necessary to furnish the hormone in a form which would be absorbed slowly over a period of several hours. If the rate of absorption had been too fast or too slow the result could have been misleading. Moreover, if the daily dose had been too small the result would have been negative. Fortunately, the first use of cortisone demonstrated to Drs. Hench, Slocumb, Polley, and me its influence on rheumatoid arthritis, and further work has added more information which confirms the early observations (Hench *et al.*, 1950; Kendall, 1950a).

A modification in the method of administration, helpful alike to physician and patient, was made when it was found that cortisone acetate can be administered orally. The daily dose required is about the same as the amount given by parenteral administration.

Chemical Specificity of Action of Cortisone

One of the first questions which were asked concerning the effect of cortisone was in regard to the chemical specificity of its action. It seemed probable that the essential functional groups in cortisone might be incorporated in some other steroid which could be prepared more easily, or that perhaps a quite different chemical structure would be as good or better. It must be admitted that some of the examples of this sort of juggling are encouraging. Diethylstilboestrol demonstrates what can be done in the family of oestrogens. Another recent contribution is the preparation of a compound which has a structure resembling that of histamine. This compound strongly stimulates gastric secretion, but is entirely free from the many other effects of histamine (Rosiere and Grossman, 1951). Cocaine simplified to "novocain" and many other examples could be given, but in the case of cortisone the problem is not so simple. The influence of cortisone has been shown to be specific; so far as we know, it is not shared with any other steroid except hydrocortisone. We also know that both cortisone and hydrocortisone are elaborated in the adrenal cortex, and appear to be the steroids which have survived the processes of selection throughout the long ages of evolution. This, of itself, is a warning that the task of finding a substitute will not be a short or an easy one (Polley and Mason, 1950).

At any rate, no substitute is known to-day, and many steroids have been tested. Unfortunately, the technique of testing has been unsatisfactory in much of this work. The patient who has rheumatoid arthritis or some other responsive disease is the only possible test object, and for the evaluation of any new product the psychic responses of both the patient and the clinician are involved. This has resulted in some disagreements, such as arose in the study of a combination of desoxycorticosterone and vitamin C. Pregnenolone, the 21-acetoxy derivative of this steroid, and the sex hormones also have enjoyed their brief interval in the limelight, but it is now generally agreed that none of these can be regarded as a substitute for cortisone (Kendall, 1950b).

Physiological Effect or Pharmacological Response?

Another question concerned the nature of the effect of cortisone: whether it could be regarded as physiological or simply as a pharmacological response to a massive dose of a steroid. A partial answer can now be given to this question. The answer is based on two aspects of the problem. The first relates to the physiological response of the adrenal cortex itself. In the recent investigations of Venning (1951), Mason (personal communication), and Corcoran *et al.* (1951) the amount of corticosteroids conjugated with glucuronic acid in the urine has been determined, as well as the amount of corticosteroids in the free form. These results indicate that from 30 to 60 mg. of corticosteroids may be excreted daily by a normal man, unaided by the administration of A.C.T.H. Since the total quantity of cortisone or hydrocortisone available is the sum of the amount produced in the adrenal cortex plus the amount administered, and since the production of cortisone in the adrenal gland is suppressed by administration of the hormone, the total amount available may come within the physiological range. Certainly, many patients who have rheumatoid arthritis are notably relieved by a daily maintenance dose of less than 60 mg. of cortisone.

The second consideration is the highly effective manner in which cortisone is delivered to the tissues by way of the secretion from the adrenal cortex, compared with the rate of absorption of the hormones when given parenterally or orally. It is impossible to determine how much of any injection is utilized effectively, but, whatever this amount may be, it is probably much less than the total. This would tend to bring the actual minimal requirements closer to physiological amounts.

The small quantity of cortisone required to bring about a remission of the symptoms of rheumatoid arthritis in some patients indicates that the normal human adrenal cortex can provide the necessary amount of its hormones. It seems probable that throughout the span of human life the adrenal cortex may provide protection during the potentially dangerous phases of a latent or subclinical attack of rheumatoid arthritis, and it would appear profitable to inquire into the activity of the anterior pituitary body and the adrenal cortex to determine whether failure on the part of either of these glands is associated with symptoms of rheumatoid arthritis.

I should like to engage in a bit of speculation to the effect that the reason the lower animals do not have rheumatoid arthritis or rheumatic fever may be that they are more adequately protected by a higher concentration of the hormones of the adrenal cortex within their tissues. Perhaps, in the evolution of mankind, a closer adjustment of the activity of the adrenal cortex results occasionally in a failure of this safeguard, and as a result rheumatic fever and rheumatoid arthritis run their course.

Nature of Rheumatoid Arthritis

From the vantage point provided by the many research projects which have been briefly reviewed, a few questions concerning the nature of rheumatoid arthritis can be answered. Rheumatoid arthritis is not an endocrine disease in the usual sense of the term. No combination of overactivity or underactivity of the ductless glands appears to be important in the aetiology of rheumatoid arthritis. Although the administration of cortisone and hydrocortisone can bring about a remission in the symptoms of rheumatoid arthritis, accompanied by a nutritional gain in weight and suppression of synovitis, these results cannot serve as a basis for the hypothesis that a deficiency of the hormones of the adrenal cortex is the cause of rheumatoid arthritis. The incidence of rheumatoid arthritis in the presence of Addison's disease is not significantly increased above that of a coincidental relationship.

There are other possibilities in a consideration of the adrenal cortex and rheumatoid arthritis. One is the effect of an alteration in the distribution of the constituents of the secretion from the gland. It has been shown that the adrenal cortex not only elaborates crystalline steroids, among which are cortisone and hydrocortisone, but that in addition important physiological activity is present in the amorphous fraction. Theoretically, it would be possible for the gland to produce excessive amounts of the amorphous fraction and insufficient amounts of cortisone and hydrocortisone. If this were true, the normal balance between the two types of hormones would be altered. The effect of cortisone might be suppressed, and the overabundance of the amorphous fraction would be unrestrained from exerting an influence which would be abnormal (Selye, 1950a, 1950b).

This hypothesis does not seem probable. The amorphous fraction is concerned with the metabolism of electrolytes, but in rheumatoid arthritis mineral metabolism is not altered significantly. Desoxycorticosterone also modifies the metabolism of electrolytes, and does so in much the same direction as does the amorphous fraction, but the administration of desoxycorticosterone to a patient who has rheumatoid arthritis does not cause an exacerbation of the symptoms, nor does it block the favourable effect of cortisone.

An observation which indicates that the symptoms of rheumatoid arthritis are not produced by abnormal amounts of the amorphous fraction has to do with the results of abrupt cessation of the administration of cortisone. It is well established that large doses of cortisone suppress the activity of the adrenal cortex. After a patient has been relieved of painful symptoms by the use of cortisone the symptoms may return within a few hours if administration of the hormone is stopped. It is not probable that the symptoms can result from a return of activity of the adrenal cortex. There may be a delay of several days before the amount of 17-ketosteroids in the urine indicates restoration of the activity of this gland (Sprague, 1950b).

Other Possible Causes

Another way in which the adrenal cortex might be the cause of rheumatoid arthritis is by the elaboration of a product not normally present. But studies thus far have not provided support for this hypothesis, since investigators frequently have found less than normal amounts of 17-ketosteroids and corticosteroids.

If some rheumatogenic agent were produced by the adrenal cortex, then stimulation of the gland should lead to an exacerbation of the symptoms. Such a demonstration would provide convincing evidence, and was one of the reasons why A.C.T.H. was administered to a patient who had rheumatoid arthritis. When this was tried for the first time at the Mayo Clinic in February, 1949, the symptoms of the disease did not become worse; on the contrary, stimulation of the gland with A.C.T.H. produced a remission of the disease (Hench *et al.*, 1950).

Since rheumatoid arthritis does not appear to be a metabolic disease caused by a disturbance in the endocrine glands, and since there are good reasons for believing that the disease is not produced by an intra-articular bacterial infection or a virus, the search for the nature of the causative agent has been directed to still other possibilities. The use of cortisone in a large number of clinical conditions has afforded results which indicate a field of research that may be fruitful. I refer to a study of the state of hypersensitivity and the phenomena associated with allergens, antigens, and antibodies, and the results of their interaction. It has been shown that cortisone can modify the effect of a large number of chemical irritants and protein antigens. For example, cortisone ameliorates the severe reaction of the tissues to salts of beryllium, and it also will lessen the response to the tuberculin reaction. Whether rheumatoid arthritis is caused by a foreign agent, such as an antigen, has not been established, but it is possible that cortisone could cause a remission in the symptoms of rheumatoid arthritis by protecting the tissues from such an agent. It could modify the rate of production of the antigen or the rate of production of an antibody, or it could protect the tissue from the effect of the products formed by combination of the antigen with the antibody. Further work in this field may yield important information concerning the aetiology and treatment of rheumatoid arthritis.

A Clinical Study

While research concerning the aetiology and optimal treatment of rheumatoid arthritis is in progress, the availability of cortisone has permitted its use by rheumatologists in the United States and to a more limited extent in other countries.

Practically 100% of patients who have active rheumatoid arthritis respond in some degree to the administration of cortisone. Furthermore, the extent of the relief has been satisfactory in a high percentage of the patients. Problems have arisen in connexion with long-continued administration of the larger amounts of the hormone which are required to control the symptoms in some patients. Recently a group of 100 patients who had rheumatoid arthritis were treated with cortisone at the Mayo Clinic. The result of the investigation furnishes an example of what can be expected at the present time in the treatment of rheumatoid arthritis with cortisone (Ward *et al.*, 1951).

Most of the patients were not admitted to hospital. Seventy-three received cortisone orally from the beginning, 27 at first received cortisone intramuscularly and then orally. Only one patient was not relieved when cortisone was given by mouth. This patient did respond when cortisone was given parenterally.

There were five objectives to the study. These were to determine: (1) the dose of cortisone required to suppress the symptoms; (2) the rate at which the initial dose could be reduced; (3) the long-term maintenance dose; (4) the effect of withholding cortisone; and (5) the percentage of patients in whom side-reactions developed.

There was a wide range (from 38 to 200 mg.) in the daily dose of cortisone required to suppress symptoms. The symptoms of a third of the patients were suppressed by 75 mg. or less, and 20% were relieved by a daily dose of 50 mg. From two days to two weeks was usually required to obtain the degree of suppression desired before reduction of the dose was started.

Dosage

In passing from the suppressive to the maintenance dose, the best results were obtained when reduction of the daily amount of cortisone was made in small decrements and at intervals of several days. The daily dose of cortisone could be reduced more rapidly for those

patients who had responded quickly to the suppressive doses. The rapidity of reduction was determined in each case by the patient's clinical—that is, the symptomatic—response, not by the sedimentation rate or other laboratory findings.

The maintenance dose was determined by two factors: reasonable control of symptoms and the occurrence of "side-effects." Eighty-six per cent. of the patients were maintained on a daily dose of 75 mg. or less, and more than half the patients received 50 mg. or less each day.

The effect of withdrawal of the hormone from most of the patients cannot be reported, since 89 of them were still under treatment as this was written. Symptoms returned in 9 of 11 cases when the administration of cortisone was deliberately discontinued. At the time of writing one of the two remaining patients had been in remission for two months; the other had been free of symptoms for ten months.

Side-effects developed in about half of the patients, but the occurrence of these effects did not necessitate discontinuation of the administration of cortisone to any patient during the study. At times the daily dose was reduced in order to control side-effects. These side-effects were related to the dose of cortisone and to the sex and age of the patients.

Busy practising clinicians are disconcerted because some patients cannot take optimal antirheumatic doses of cortisone indefinitely, and because symptoms return when the use of the hormone is discontinued. Therefore they raise, somewhat prematurely, questions concerning the longe-range value of cortisone as a therapeutic agent. But the fact that rheumatic symptoms are suppressed by cortisone and return when cortisone is withheld has provided a challenge to clinical investigators which they expect to meet and solve by more study. At the present time many questions have been answered satisfactorily. Some questions remain to be answered, but the advances in our understanding of rheumatoid arthritis which have come during the past three years lend assurance that further research will be well repaid (Sprague, 1950a; Sprague *et al.*, 1950).

In the acute phase of rheumatic fever cortisone will abolish the symptoms, and it seems to protect the heart from damage. Whether cardiac changes will occur after the acute phase has passed will not be known for some years, but the results to date are encouraging.

Conclusion

The two syndromes—rheumatoid arthritis and rheumatic fever—are not far separated in their nature and in their response to cortisone. Similar comparisons hold for some of the other collagen diseases. Perhaps the most hopeful aspect of the study is the wide portion of clinical medicine which is influenced by this hormone. The unexpected and far-reaching influence of cortisone on many diseases may be produced through its control of some causative agent which is common to all of them. The nature of this agent is unknown, but I agree with Professors Pickering (1950) and Meiklejohn (1950) that the hypothesis of the adaptation syndrome of Selye (1950a, 1950b) is not acceptable.

To-day it can be said that cortisone will relieve the pain and symptoms of rheumatoid arthritis, and it constitutes a life-saving measure for other syndromes, but to the clinician interested in research it will be a key which will unlock the doors of barriers and reveal secrets long hidden.

References

Corcoran, A. C., Dustan, H. R., and Page, I. H. (1951). *Abstr. Meet. Amer. Soc. clin. Invest.*, Atlantic City.
Hench, P. S. (1949). *Ann. rheum. Dis.*, **8**, 90.
—— (1950). *Les Prix Nobel.* Norstedt, Stockholm.
—— Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 545.
Kendall, E. C. (1950a). *Ann. intern. Med.*, **33**, 787.
—— (1950b). *Les Prix Nobel.* Norstedt, Stockholm.
—— *et al.* (1946–51). *J. biol. Chem.*, **162**, **164**, **166**, **173**, **175**, **185**, **188**, **190**.
Meiklejohn, A. P. (1950). *Lancet*, **2**, 154.
Pickering, G. W. (1950). Ibid., **2**, 81.
Polley, H. F., and Mason, H. L. (1950). *J. Amer. med. Ass.*, **143**, 1474.
Reichstein, T., and Shoppee, C. W. (1943). In Harris and Thimann's *Vitamins and Hormones*, **1**, 345.
Robinson, Sir Robert (1951). Paper presented at Meeting of the Amer. Chem. Soc., New York City, September, 1951.
Rosiere, C. E., and Grossman, M. I (1951). *Science*, **113**, 651.
Sarett, L. H. (1948). *J. Amer. chem Soc.*, **70**, 1454.
Selye, H. (1950a). *Stress.* Acta, Inc., Montreal.
—— (1950b). *Amer. J. Med.*, **10**, 549.
Sprague, R. G. (1950a). Ibid., **10**, 567.
—— (1950b). In Harris and Thimann's *Vitamins and Hormones*, **9**, in press.
—— Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, F. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 199.
Venning, Eleanor, H. (1951). *Abstr. Papers Program Ass. Study Internal Secretions*, June.
Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S. (1951). *Proc. Mayo Clin.* In press.
Wendler, N. L., Huang-Minlon, and Tishler, M. (1951). *J. Amer. chem. Soc.*, **73**, 3818.
Woodward, R. B., Sondheimer, F., and Taub, D. (1951). Ibid., **73**, 4057.

THE INFLUENCE OF UNILATERAL NEPHRECTOMY ON THE PRODUCTION OF EXPERIMENTAL ARTHRITIS IN THE ALBINO RAT

BY

R. G. HARRISON, D.M.

Derby Professor of Anatomy, University of Liverpool

[WITH SPECIAL PLATE]

The production of an acute mono- or poly-arthritis by repeated injections of deoxycortone acetate (D.C.A.) has been demonstrated by Selye *et al.* (1944) in rats subjected to removal of the left kidney and given 1% saline to drink. Outside Selye's own laboratory this finding has been confirmed by Pirozynski and Akert (1949). Other investigators (Harrison, 1946; Kuzell, personal communication) using Selye's methods were, however, unable to produce arthritis in rats. Selye (1946a) at first suggested that this may have been due to feeding the rats a diet inadequate in protein content; more recently (Selye, 1950) he has stated that the cause of the "inconstancy in the production of arthritis by D.C.A. has not yet been elucidated, but presumably it depends upon the presence of conditioning factors such as some local irritant."

In view of this inconstancy and the discrepancy between the results of different investigators, it was decided to reinvestigate the problem. Since in the original experiments (Harrison, 1946) it was possible to control all of the experimental techniques used by Selye *et al.* (1944) except that of nephrectomy, it seemed that the manner of performing this operation might be a possible cause of the discrepancy. This supposition appeared more likely since it has been shown (Harrison, 1951) that interruption of an adrenal artery in the rat or rabbit results in an area of necrosis

in the zona fasciculata of the adrenal cortex; in immature rats, such as those used by Selye *et al.* (1944) in their experiments, one, or sometimes two, adrenal arteries of variable size are found arising from the left renal artery, in addition to those seen in the adult arising from the aorta (Harrison, 1951: Text—Fig. 2). In removing the left kidney of a rat, it would not be difficult to interrupt such functional anatomical channels inadvertently when ligating the renal pedicle, with resultant necrosis of part of the zona fasciculata of the adrenal cortex. The following investigation was therefore designed to estimate the effect of deliberate interruption of adrenal arteries arising from the left renal artery on the production of experimental arthritis in the rat, in view of the importance of cortisone, a secretory product of the adrenal cortex, in the therapy of rheumatoid arthritis.

Experimental Methods

Thirty albino rats, varying in weight from 30 to 55 g., were used for the experiment. The rats were obtained from a Wistar strain colony, inbred for seven years. Three or six rats from each litter were arranged so as to provide three groups of ten litter-mate rats. The average body weight in the three groups of rats was 42.5, 41.8, and 40.2 g. respectively. The left kidney of rats of group I was removed, carefully avoiding the adrenal vein and any branches arising from the renal artery, after placing a ligature around the pedicle close to the hilum, as in the previous experiments (Harrison, 1946). In rats of groups II and III the pedicle of the left kidney was seized with fine curved artery forceps so as to include the inferior adrenal arteries, and the kidney then removed; all the inferior adrenal arteries which may arise from the renal artery were severed in this procedure.

Rats in all three groups were given 1% saline to drink instead of tap-water throughout the experiment, and were fed on a diet similar in composition to "purina fox chow." From the fifth day after operation animals of groups I and II were injected with 2 mg. of finely ground D.C.A. crystals subcutaneously, twice daily, from an aqueous suspension containing 20 mg. of D.C.A. per ml. and 0.1% cetrimide (which was added in order to increase the degree of dispersion of the crystals in suspension and thereby facilitate their injection and constancy of dosage). Animals of group III received an injection of 0.1 ml. of 0.1% cetrimide in water twice daily. Injections were continued for a period of twenty days, when all animals in groups I and II were killed. Individual rats in group III were killed at three-day intervals following operation.

Signs of arthritis were looked for in all four limbs of each rat at the time of each injection. The adrenals of all rats were removed at necropsy, and, after fixation in Zenker-formol, or Baker's (1944) formal-calcium, serial sections of the adrenals were stained or coloured with Heidenhain's iron haematoxylin and eosin, Sudan black for total lipoids, Schultz's method of application of the Liebermann-Burchardt reaction for cholesterol and its esters, or Baker's (1946) acid haematein technique for phospholipines. The joints were embedded in low-viscosity nitrocellulose (Chesterman and Leach, 1949), and 18-μ sections were stained with Ehrlich's haematoxylin and eosin or Gram's method for bacteria.

The room in which the animals were kept was not thermostatically heated, but the experiments were performed during the period June 22–July 17, 1951, when maximum and minimum temperatures in the shade were 70.2 and 48.2° F. (21.2 and 9° C.) respectively, the mean daily temperature being 57.9° F. (14.4° C.). The relative humidity during this period varied between 70.1 and 96.0, the mean being 79.4.

Results

Two rats in group I died on the 8th and 18th days of the experiment, when the adrenals were found to show gross haemorrhage into the cortex, with large areas of haemorrhagic necrosis, involving all the cortical zones. Two rats in group II also died, on the 21st and 23rd days of the experiment, from no obvious cause, except that the former had presented marked ascites from the 17th day of the experiment. Slight ascites was also found in one rat of group I at necropsy, when all rats of group I and seven rats of group II were found to have some degree of enlargement of the liver; the liver was equally enlarged, however, in the two rats of group III killed on the last day of the experiment.

FIG. A.—Appearance of the hind-foot in a control rat (group III).

FIG. B.—Marked swelling of the left ankle-joint in a rat of group II (rat 19) on the 19th day of the experiment.

On the 19th day of the experiment (the 14th day after initiation of D.C.A. injections) one rat (rat 19) in group II had obvious arthritis in its left ankle-joint (Figs. A and B); this increased to a maximum on the 21st day, when the other ankle-joint also became involved, and then regressed slightly until the termination of the experiment, by which time, however, the joints of the forepaws had become affected. On the 23rd day two more rats in group II showed arthritis, one (rat 16) in the right ankle-joint (Fig. C), and the other (rat 18) in the left tarsal joints (Fig. D); this became pronounced by the next day, only to regress slightly by the last day of the experiment. In all cases the arthritis presented as a tender swelling with redness of the overlying skin and limitation of movement. On the 22nd day of the experiment two rats in group I also developed arthritis. In one (rat 5) the arthritis appeared to involve the left ankle and tarsal joints only very slightly; by the next

day the tarsal joints of the other foot had become slightly affected, but at the end of the experiment all signs of arthritis had almost disappeared. In the other rat (rat 6) the left ankle and tarsal joints were slightly involved. The arthritis in these two rats was undoubtedly much less severe than in the arthritic rats of group II.

On examination of the adrenals it is found that all arthritic rats, whether of group I or II, show an area of necrosis in the cortex of the left adrenal gland. In rat 19 there is a large area of necrosis involving the whole width of the zona fasciculata (Fig. 1, on Special Plate), except for a few cells in the outermost part of this zone, the zona glomerulosa being unaffected. In rat 16 there is an area of necrosis in the deeper part of the zona fasciculata near the exit of the adrenal vein, the outer part of the zona fasciculata and the zona glomerulosa being quite normal in appearance. In rat 18 (Fig. 2) the appearance of the adrenal cortex is similar to that in rat 19, except that the cells of the zona glomerulosa show confluence of their cytoplasm to form a syncytium over most of the area of necrosis.

FIG. C.—Appearance of the ankle-joint in another rat of group II (rat 16) on the 23rd day of the experiment.

FIG. D.—Swelling of the left foot over the tarsal joints in rat 18 on the 23rd day of the experiment.

In the arthritic rats of group I, rats 5 and 6 have an area of focal necrosis in the left adrenal cortex which involves only the outer part of the zona fasciculata and affects the zona glomerulosa only slightly. Common to all the arthritic rats, therefore, is an area of focal necrosis restricted to the zona fasciculata of the cortex of the left adrenal gland. Although great care was taken at operation to avoid all branches of the left renal artery in rats of group I, it was evident at necropsy that the inferior adrenal arteries had become constricted by fibrous tissue resulting from the nephrectomy in rats 5 and 6; this would probably account for the cortical necrosis in these rats. This was also the case in three other rats of group I, but the necrotic areas in these rats involved both the zona glomerulosa and the zona fasciculata; the remainder of the rats in group I showed no focal necrosis of the adrenal cortex.

All the non-arthritic rats of group II showed areas of cortical necrosis, but, as in the three rats of group I just mentioned, they were very different from the necrosis in arthritic rats, since they involved either the whole width of the adrenal cortex (Fig. 3) or the whole extent of the zona glomerulosa over the surface of the lesion as well as the zona fasciculata. The differences in extent and character of the lesions in arthritic and non-arthritic rats appeared to be conditioned by the degree of ischaemia. The branches of the left renal artery supplying the lower pole of the adrenal vary from a single vessel, little larger than an arteriole, to two well-developed arteries. Interference with the former produces a small lesion entirely restricted to the zona fasciculata which would only involve the zona glomerulosa at a much later date, if at all, while interruption of the latter produces at first two large areas of focal necrosis in the zona fasciculata which would later coalesce and then rapidly involve the zona glomerulosa.

The histological appearance of the arthritic joints is very similar to that in the experiments of Selye *et al* (1944). The synovial villi show some oedema and often desquamation of mesothelial cells, with development of granulation tissue in periarticular structures (Fig. 4). There is no ulceration of articular cartilages, and no bacteria could be detected in periarticular structures or in the transudate which can be found in the cavities of affected joints. Occasionally hyalinization of subsynovial tissue can be seen.

Histochemistry of the Adrenal Cortex

In rats of all groups the zona glomerulosa is free of lipoid, phospholipine, and cholesterol. This is in agreement with the findings of Greep and Deane (1947) and Deane and Masson (1951) that D.C.A., or saline treatment alone, leads to lipoid depletion of this zone. The zona reticularis and inner zona fasciculata are also depleted of phospholipine in the arthritic rats, but phospholipine is present in the outer one-third to one-half of the zona fasciculata (Fig. 2); the appearance is identical in both adrenals, except that the necrotic zone in the left adrenal contains phospholipine only in a few cells immediately underneath the zona glomerulosa. The distribution of lipoids, as shown by Sudan black, differs from that of phospholipine in the adrenals of arthritic rats. Whereas the heaviest loading of lipoid appears to be in the outer part of the zona fasciculata (Fig. 1) and in that region corresponding to the distribution of phospholipine, the cytoplasm of all other cells in the zona fasciculata, and even the zona glomerulosa, contains very fine droplets of lipoid. In the zona reticularis larger globules can be seen in addition to these fine droplets. While the necrotic zone is free of lipoid, there are large, irregular masses of lipoid at the periphery of the zone caused by liberation and confluence of globules from cells undergoing degeneration (Fig. 5). Such globules are negative in the test for phospholipine, but do contain cholesterol (Fig. 6); this region is, in fact, the only part of the cortex in the adrenals of arthritic rats which is positive to the Schultz reaction.

The adrenal cortex of non-arthritic rats of group II, however, does show a faintly positive reaction in the Schultz test. The fine granules of cholesterol are present in cells of the outer part of the zona fasciculata, and are scattered throughout the cytoplasm quite regularly. The area of focal necrosis is depleted of cholesterol. The distribution of lipoid in non-arthritic rats of groups I

and II is similar to that in the arthritic rats, except that almost the whole width of the zona fasciculata shows a uniform heavy loading of this substance; the very fine droplets of lipoid are less obvious, particularly in the zona glomerulosa. The zona reticularis is, on the whole, much more reticular in appearance, owing to more pronounced dilatation of the sinusoids in this region, and contains more lipoid than in the arthritic rats. The necrotic zone in rats of group II is depleted of lipoid except for the large confluent extracellular globules, which are dense black in appearance.

The adrenal cortex of the arthritic rats is therefore characterized by absence of cholesterol, although a small amount of cholesterol-positive but phospholipine-negative extracellular lipoid liberated by degenerating cells is found in the area of necrosis which itself contains no lipoid or cholesterol and very little phospholipine. Droplets of finely divided lipoid are scattered in the zona glomerulosa, zona reticularis, and inner zona fasciculata, and phospholipine is found only in the outer zona fasciculata. This is an appearance not encountered in the normal rat (Harrison and Cain, 1947; Cain and Harrison, 1950), and, since it differs from that in the other litter-mate rats which do not show macroscopic evidence of arthritis in these experiments, can be taken as characteristic of rats rendered arthritic by the technique used here.

Discussion

The above experiments suggest that a contributory factor in the production of arthritis in rats injected with large doses of D.C.A. and given 1% saline to drink is necrosis of the adrenal cortex restricted to the zona fasciculata. This can be produced by unilateral nephrectomy either by inadvertently interrupting adrenal arteries during the operation or by the involvement of the latter in fibrous tissue resulting from the operation. The necrosis of the adrenal cortex probably accounts for the increase in weight of the contralateral adrenal following unilateral nephrectomy (Fichtelius *et al.*, 1948).

Selye *et al.* (1944) claim that thyroidectomy also increases the liability to production of arthritis in their experiments. This operation has been shown (Deane and Greep, 1947) to cause atrophy of only the zona fasciculata of the rat adrenal cortex. Intravenous injection of a culture of *Streptococcus haemolyticus* similarly facilitates the appearance of arthritis in rats injected with D.C.A. (Haour, 1949); Mitchell and Angrist (1943) have reported that focal necrosis of the adrenal cortex due to a variety of infectious disease processes is mainly encountered in the zona fasciculata.

While unilateral nephrectomy is therefore one of several factors which may lead to degeneration of the zona fasciculata of the adrenal cortex, its added effect on sodium balance, for example, cannot be excluded; the relatively minor importance of the latter factor in the aetiology of arthritis in these experiments, however, is suggested by the fact that arthritis did not develop in any of the unilaterally nephrectomized rats which did not have an area of focal necrosis in the adrenal cortex.

It is essential, therefore, to consider the practical importance of such a disturbance of the zona fasciculata for the aetiology of arthritis. In the rat, histochemical and cytological evidence (Deane and Greep, 1946; Harrison and Cain, 1947; Jones, 1949; Cain and Harrison, 1950) indicates that the three zones of the adrenal cortex exhibit relative morphological and functional independence; examination of the vascularization of the adrenal cortex confirms this impression (Harrison, 1951). Whereas the salt-regulating fractions of adrenal cortical secretion—for example, deoxycortone—are formed in the zona glomerulosa, the carbohydrate-regulating principles—that is, the 11-keto- or hydroxy-corticosterones, such as cortisone—are secreted by the zona fasciculata. Any necrosis of the zona fasciculata would therefore lead to diminished production of the carbohydrate-regulating hormones, and a dissociation of the normal relationships of gluco-corticoid and mineralo-corticoid secretion. This would be enhanced by repeated injections of D.C.A. A primary reduction of gluco-corticoid secretion caused by focal necrosis of the zona fasciculata of the adrenal cortex therefore seems to be an important factor in the production of experimental arthritis in rats. This would account for the "sensitizing" action of unilateral nephrectomy, at least in part, and provides an experimental rationale for the formerly rather empirical therapy of arthritis with cortisone.

Selye *et al.* (1944) and Pirozynski and Akert (1949) claim that bilateral adrenalectomy facilitates the production of arthritis in rats treated with D.C.A. Owing to the presence of accessory cortical nodules in the rat, bilateral adrenalectomy is notoriously ineffective in removing all cortical tissue. Further, since such cortical rests often consist of cells arranged in glomerular formation (Jaffe, 1927), it is possible that bilateral adrenalectomy also leads to preponderant or absolute mineralocorticoid secretion, augmented again by repeated injections of D.C.A. Chamorro (1945) has reported the occurrence of arthritis in bilaterally adrenalectomized rats receiving no treatment, but Selye (1950) has not seen arthritis in otherwise untreated adrenalectomized rats; nor was arthritis encountered in a series of 90 female rats, varying in weight from 27 to 126 g., subjected to bilateral adrenalectomy and ovariectomy (Harrison, unpublished observations), though ovariectomy increases the percentage of rats developing arthritis as a result of D.C.A. treatment (Haour, 1949). In Chamorro's (1945) experiments arthritis occurred only in rats which survived adrenalectomy 14 days or longer, which would indicate either that the operation was incomplete or that his rats possess large amounts of accessory cortical tissue, with consequent imbalance of adrenal cortical secretion.

The role of infection in the aetiology of experimental arthritis in the rat must be considered in these experiments. Thus, Pemberton *et al.* (1947) found that the experimental methods of Selye *et al.* (1944) did not lead to joint changes with a frequency greater than in their control rats, which were found to have histological evidence of arthritis. This spontaneous arthritis would undoubtedly complicate their results, for the articular cartilages of both control and experimental rats showed destruction or replacement by proliferating connective tissue, with adhesions between the articular surfaces; none of these histological changes were found in Selye's experiments, and it would therefore be difficult to interpret the changes resulting from hormonal interference when superadded to these destructive lesions. Infection, however, may be directly or indirectly concerned with the production of rheumatic cardiac lesions and nephrosclerosis (Harrison, 1946), which, together with arthritis, are included in the "diseases of adaptation" (Selye, 1946b).

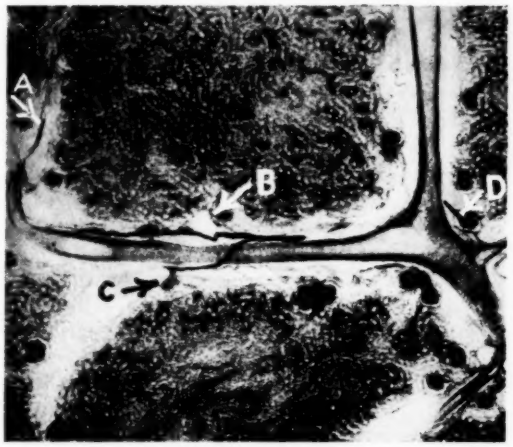


FIG. 1.—A nerve trunk running along a renal artery to its termination. It supplies tubules (B) and glomerulus (C). (×32.)

FIG. 2.—Glomerulus C of Fig. 1: nerve plexus round it. One thick nerve fibre and many thin nerve fibres run along its afferent artery. (×375.)

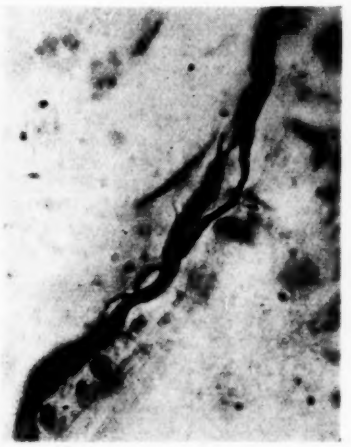


FIG. 3.—A thick nerve fibre (A in Fig. 1) running along the termination of a renal artery, giving an "end foot." (×850.)

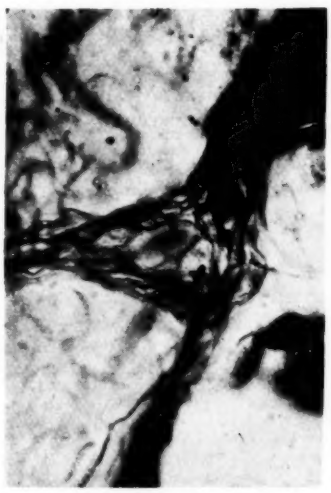


FIG. 4.—Nerve fibres and nerve endings round nerve cells, inside the rat kidney. Microganglion. (Silver.) (×1,990.)

FIG. 5.—A ganglion on a branch of the renal artery. Human kidney. (Silver.) (×310.)

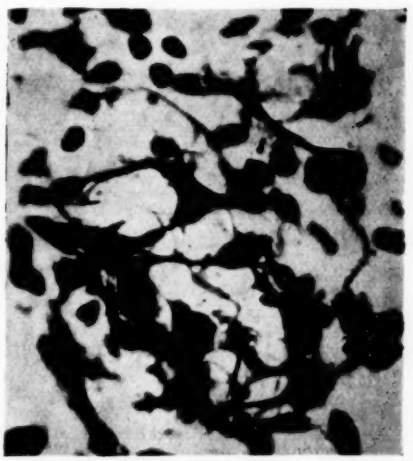


FIG. 6.—Multipolar cells and nerve fibres and endings inside a glomerulus. Rabbit kidney. (Gold.) (×1,050.)

FIG. 7.—Multipolar cell with two processes round a capillary wall cell. Mouse kidney. (Silver.) (×2,350.)

FIG. 8.—Spiral filament of the multipolar cell (Fig. 7) round a capillary inside a glomerulus. Mouse kidney. (Silver.) (×2,350.)

FIG. 9.—A polyhedral cell inside a glomerulus with a comma-shaped process and another (cut) comma-shaped process. (×2,350.)

Z. M. EL ASFOURY: SYMPATHECTOMY AND INNERVATION OF KIDNEY

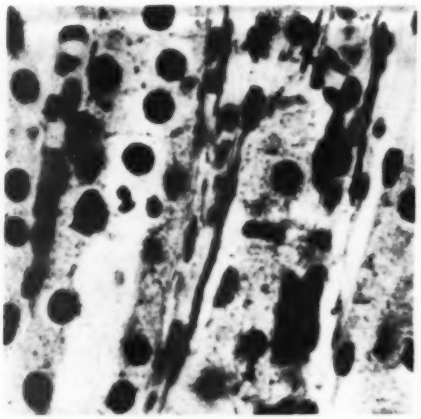


FIG. 10.—Intertubular polyhedral cell and nerve fibres. Rabbit kidney. (Silver.) (×1,050.)

FIG. 11.—Reticulum between the renal tubules, for comparison with Fig. 10. Cat kidney. (Silver.) (×525.)

FIG. 12.—Ganglion: nerve-cell fibres in the renal papilla. Rat. (Silver.) (×2,389.)

R. G. HARRISON: UNILATERAL NEPHRECTOMY IN RAT

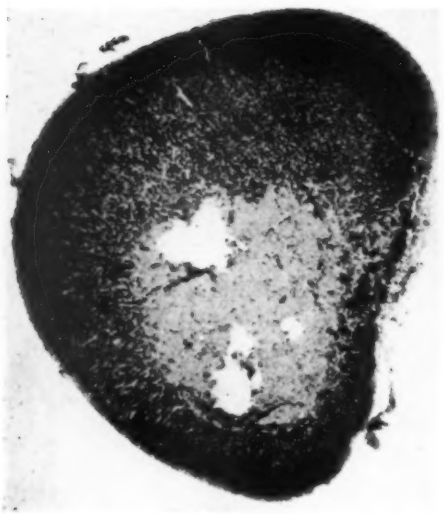


FIG. 1.

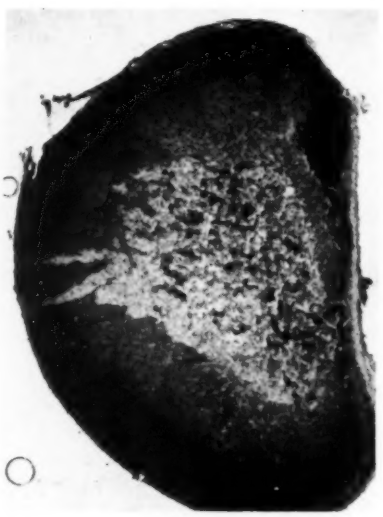


FIG. 2.

FIG. 3.

FIG. 4.

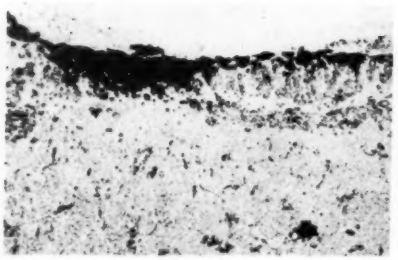


FIG. 5.

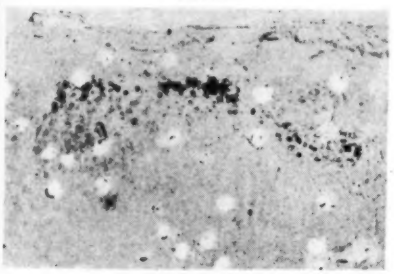


FIG. 6.

FIG. 7.

Spontaneous arthritis due to a corynebacterium can also occur in the rat (Fischl, Koech, and Kussat, 1931), and such a corynebacterium was isolated from the lungs of a rat suffering from spontaneous non-pyogenic arthritis in a colony of about 200 rats, which produced arthritis when injected intraperitoneally in another rat (Vollum and Harrison, unpublished observations). The appearance of the arthritis in these rats (Fig. E) is very similar to that following D.C.A. injections, but the course of the affection differs: whereas that seen following D.C.A. treatment is characteristically transient, often fleeting, the arthritis due to *Corynebacterium arthritidis muris* is progressive and unremitting, the rat often developing an intercurrent infection. Uehlinger, Akert, and Pirozynski (1950) state that the arthritis caused by D.C.A. overdosage is not prevented by streptomycin treatment, although this does not entirely exclude an infectious element in the aetiology of arthritis by certain bacterial agents. It is possible, therefore, that there are two different types of disease process in the rat—the "diseases of adaptation" caused by hormonal imbalance, and various similar lesions, which may be spontaneous, produced by infection; on the other hand, some systemic infections "are among the most potent stressor agents in clinical medicine" (Selye, 1950), and consequently it is possible that there may be a non-specific response of the adrenal cortex common to both processes.

It is difficult to apply the results of these experiments unconditionally to the problems of arthritis in man. There are, however, various agents which could lead to diminished function of the zona fasciculata of the human adrenal cortex. A variety of infectious and toxic processes can cause loss of lipoid from and focal necrosis or sclerosis of only this zone (Bernard and Bigart, 1906; Hoerr, 1931; Mitchell and Angrist, 1943; and others). It is also possible that a sustained vasoconstriction of adrenal arteries could produce focal necrosis of the adrenal cortex, particularly since the peripheral vessels in patients with rheumatoid arthritis are easily constricted (Naide, Sayen, and Comroe, 1945). Such focal necrosis or diminution of adrenal cortical lipoid could be detected only in the acute stages of the disease; the end-result of focal necrosis, for example, is a small area of fibrous tissue which could easily be mistaken for a fibrous-tissue septum within the cortex. Once such a disturbance of the zona fasciculata has occurred, additional oversecretion of mineralo-corticoids may lead to arthritic manifestations. A further difficulty in applying to man these results in the rat is the apparent lack of absolute correlation of function with zone morphology in the human adrenal cortex; the human zona fasciculata and zona glomerulosa may nevertheless show a preponderant secretion of gluco-corticoids and mineralo-corticoids respectively, the difference between the rat and man being merely one of degree.

FIG. E.—The hind limbs of a male rat which developed arthritis spontaneously in its left hind foot and from whose lungs was isolated a bacterium similar in characteristics to *Corynebacterium arthritidis muris*.

It is possible that the time relations of the experimental procedures in this investigation are of some significance. Thus, five days after removal of the left kidney, when D.C.A. injections are initiated, the necrotic lesion in the zona fasciculata is well marked and at a stage in which the cortical cells are disintegrating to liberate globules of lipoid (Fig. 7). At this point the imbalance of adrenal cortical secretion may be just appearing, to provide a condition most susceptible to D.C.A. overdosage.

The other diseases of adaptation will be considered in a further communication.

Summary

The production of arthritis has been studied in rats subjected to removal of the left kidney, given 1% saline to drink, and injected with D.C.A.

It is suggested that the "sensitizing" effect of the unilateral nephrectomy is by virtue of a focal necrosis of the zona fasciculata of the adrenal cortex due to interference with adrenal arteries and resultant reduction in the secretion of gluco-corticoids. This provides experimental confirmation for the therapy of arthritis with cortisone.

The histochemical appearance of the adrenal cortex of arthritic rats is described.

The effect of other experimental techniques and infection on the production of hormonally induced arthritis in the

R. G. HARRISON: LEGENDS TO PLATE

FIG. 1.—Photomicrograph of a section of the left adrenal of rat 19. Sudan black. The area of necrosis is seen in the zona fasciculata on the right-hand side of the figure. The zona glomerulosa is seen as a rim of cells relatively free from lipoid around the periphery of the cortex and extending intact over the surface of the lesion in the zona fasciculata. The heaviest loading of lipoid is in the outer part of the zona fasciculata. (×20.)

FIG. 2.—The left adrenal of an arthritic rat (rat 18). Acid haematein method. The necrotic lesion is on the right-hand side of the figure; the medulla extends almost to the surface of the gland at this point, being separated only by a few degenerating cells of the zona fasciculata and an intact zona glomerulosa. The zona glomerulosa is almost free of phospholipine, the main distribution of which is restricted to the outer zona fasciculata (dark coloration). Phospholipine is also seen to be present in the outer part of the zona fasciculata immediately under the zona glomerulosa; this is intracellular and not in the extracellular globules of lipoid. (×20.)

FIG. 3.—Complete destruction of all cortical zones in the area of necrosis (right-hand side of figure) in the left adrenal cortex of a non-arthritic rat of group II. Iron haematoxylin and eosin. (×18.)

FIG. 4.—The ankle-joint of an arthritic rat (rat 19), showing the infiltration of periarticular structures with granulation tissue in the bottom left-hand corner of the figure. (×20.)

FIG. 5.—The globules of free lipoid liberated by degenerating cells in the zona fasciculata of the left adrenal cortex of rat 19, which show as black masses in this figure. Sudan black. (×50.)

FIG. 6.—A section of the left adrenal cortex of rat 19 from a comparable region to that in Fig. 5, showing the distribution of cholesterol, which is seen here as black particles in the same location as the free lipoid. (×50.)

FIG. 7.—The left adrenal cortex of a control rat five days after left unilateral nephrectomy in which a single artery supplying the inferior pole of the adrenal was interrupted. The necrotic lesion, composed of disintegrating cells which are liberating their lipoid, can be seen as the dark area in the upper part of the figure. Sudan black. (×22.)

rat is considered, and an assessment made of the relationship of this experimental arthritis to the aetiology of human arthritis.

I am indebted to Dr. W. J. Tindall, of Organon Laboratories Ltd., for the supplies of D.C.A. used in these experiments, and to the Ralston Purina Company for providing particulars of, and Lever's Cattle Foods, Ltd., Bebington, Cheshire, for manufacturing, a diet similar in composition to "purina fox chow." I also wish to thank Mr. L. G. Cooper for his technical assistance.

REFERENCES

Baker, J. R. (1944). *Quart. J. micr. Sci.*, **85**, 1.
—— (1946). Ibid., **87**, 441.
Bernard, L., and Bigart, M. (1906). *J. Physiol. Path. gén.*, **8**, 84.
Cain, A. J., and Harrison, R. G. (1950). *J. Anat., Lond.*, **84**, 196.
Chamorro, A. (1945). *C.R. Soc. Biol., Paris*, **139**, 589.
Chesterman, W., and Leach, E. H. (1949). *Quart. J. micr. Sci.*, **90**, 431.
Deane, H. W., and Greep, R. O. (1946). *Amer. J. Anat.*, **79**, 117.
—— —— (1947). *Endocrinology*, **41**, 243.
—— and Masson, G. M. C. (1951). *J. clin. Endocrinol.*, **11**, 193.
Fichtelius, K.-E., Garby, L., Linder, L., and Stahle, J. (1948). *Acta anat., Basel*, **4**, 410.
Fischl, V., Koech, M., and Kussat, E. (1931). *Z. Hyg. InfektKr.*, **112**, 421.
Greep, R. O., and Deane, H. W. (1947). *Endocrinology*, **40**, 417.
Haour, P. (1949). *Rev. Rhum.*, **16**, 466.
Harrison, R. G. (1946). *Lancet*, **1**, 815.
—— (1951). *J. Anat., Lond.*, **85**, 12.
—— and Cain, A. J. (1947). Ibid., **81**, 286.
Hoerr, N. (1931). *Amer. J. Anat.*, **48**, 139.
Jaffe, H. L. (1927). *Arch. Path.*, **3**, 414.
Jones, I. C. (1949). *Endocrinology*, **45**, 514.
Mitchell, N., and Angrist, A. (1943). *Amer. J. med. Sci.*, **205**, 549
Naide, M., Sayen, A., and Comroe, B. I. (1945). *Arch. intern. Med.*, **76**, 139.
Pemberton, R., Eiman, J., Patterson, F. M. S., and Stackhous, E. A. (1947). *J. Lab. clin. Med.*, **32**, 1121.
Pirozynski, W., and Akert, K. (1949). *Schweiz. med. Wschr.*, **79**, 745.
Selye, H. (1946a). *Lancet*, **1**, 942.
—— (1946b). *J. clin. Endocrinol.*, **6**, 117.
—— (1950). *Stress*. Acta Inc., Montreal
—— Sylvester, O., Hall, C. E., and Leblond, C. P. (1944). *J. Amer. med. Ass.*, **124**, 201.
Uehlinger, E., Akert, K., and Pirozynski, W. (1950). *Bull. schweiz. Akad. med. Wiss.*, **6**, 157.

SYMPATHECTOMY AND THE INNERVATION OF THE KIDNEY*

BY

Z. M. EL ASFOURY, B.Sc., M.R.C.S., L.R.C.P.

(From the Department of Anatomy, London Hospital Medical College)

[WITH SPECIAL PLATE]

The innervation of the kidney has recently attracted some attention because of its possible importance in the study of renal physiology and pathology, and more particularly in the study of the problem of hypertension. Many early workers investigated the nerve supply to the kidney, but until lately their observations have been largely neglected.

Among the investigators who have contributed to this subject are Holbrook (1883), Kölliker (1893), Berkley (1893a, 1893b), and others whose work was reviewed by Stöhr in 1928.

More recently Kaufmann and Gottlieb (1931) showed that the kidney parenchyma has a rich innervation. De Muylder (1940, 1945, 1948) has stressed that myelinated nerve fibres as well as non-myelinated nerve fibres can be found in the kidney. He also recorded "sensitive corpuscles" in intimate relation with branches of the renal veins. Mitchell (1947, 1950) published papers on the innervation of the kidney and its significance. Harman and Davies (1948) confirmed certain aspects of the earlier work.

Material and Methods.—Normal kidneys of foetal and adult mouse, frog, rat, rabbit, cat, and human were examined. Various methods of staining, including metallic impregnation and organic dyes, were used to stain nerve fibres and nerve cells. Staining for reticulum was also widely used to compare results obtained by the other staining procedures.

Untouched photomicrographs were obtained from the material.† Diagrams were also prepared from groups of photomicrographs taken at different foci for the same field in thick preparations.

Personal Findings

In addition to confirming certain observations of previous investigators, I believe that the following points are demonstrated by my material.‡ (Asfoury, 1950.)

FIG. A.—Diagram made from photomicrographs like Fig. 2, at different foci, showing a nerve plexus round a glomerulus. There are few thick and many thin nerve fibres. Club-shaped nerve endings are seen on the afferent arteriole.

The kidney receives a rich nerve supply, running along the main renal blood vessels as they enter the hilum. The nerve fibres follow the branches of the vessels to their terminations. During their course, however, some nerve fibres leave the blood vessels to supply the tubules, the glomeruli (Plate, Fig. 1, B and C), and the pelvis.

The nerve fibres vary in thickness and intensity of staining. A few fibres are very thick and irregular in outline. They can be shown with a myelin stain—for example, osmic acid. Such fibres tend to run separately inside the kidney. Some of these fibres appear to give off "end feet" on their course (Fig. B and Plate, Fig. 3). These thick fibres are also present in the rich plexuses around the blood vessels and glomeruli (Fig. A and Plate, Fig. 2).

*Abridged from a lecture given to the Renal Association of Great Britain on October 26, 1950.

†Only a few untouched photomicrographs are shown here; the rest were shown as such or as lantern slides before and during the lecture.

‡Numerous slides and diagrams were available for inspection before and after the lecture.

FIG. B.—Diagram of Fig. 3.

The remaining and more common renal nerve fibres are thinner, but they vary from medium to very thin in calibre. Some of them appear brown, while others appear jet black, in the same silver preparation.

Nerve Cells Inside the Kidney.—Groups of nerve cells forming ganglia are present along the blood vessels inside the kidney tissue. These ganglia vary in size from quite large groups, with many cells, to small groups of only a few nerve cells. All of these nerve cells appear to be surrounded by synaptic formations (Fig. C. and Plate, Figs. 4 and 5).

Nerve Cells in the Renal Papilla.—The renal papilla has a rich nerve supply, and ganglion cells are present in it (Fig. 12).

Polyhedral Cells in Relation to Glomeruli.—Polyhedral cells are present inside the glomeruli lying directly on the walls of the capillaries (Fig. 7). They send out protoplasmic processes which end in long filaments. These filaments wind themselves round the capillaries in a spiral form (Fig. 8), and they seem to end on the nuclei of the capillary cells near or on their nucleoli (Fig. D). These cells are numerous, and their processes are in intimate contact with each other. Other polyhedral cells have comma-shaped processes between the glomerular capillaries (Figs. 9 and E).

Polyhedral Cells Between the Tubules.—Between the renal tubules there are cellular elements which are often called "interstitial cells." Some of these are polyhedral argentophil cells whose fibres end on certain of the tubule cells. Nerve fibres end in relation to these intertubular-polyhedral cells (Fig. 10). Appearances of neurofibrils are often to be found in the protoplasm of these intertubular cells. Other so-called interstitial cells are undoubtedly fibroblasts.

FIG. D.—Diagram made from Figs. 7 and 8.

The Capsule of the Kidney.—Nerve fibres run along the capsular blood vessels; subcapsular nerve fibres show the same variation in thickness and intensity of staining as the fibres inside the kidney. Some of them run parallel to the subcapsular cells while others run across them.

Schwann Cells.—These are seen in relation to many of the renal nerve fibres.

The above-mentioned polyhedral cells have the following histological characters: (1) They are argentophil. (2) Their protoplasm extends into processes as in nerve cells (Fig. 6). (3) In both protoplasm of cell body and in the processes neurofibril-like structures are present. (4) The use of reticular fibre stain shows that these cells and their fibres are different from reticular fibres and their associated cells (Fig. 11). (5) There seems to be histological evidence for the existence of synapse-like communications between the nerve fibres and the cell bodies of the presumed nerve cells or their processes.

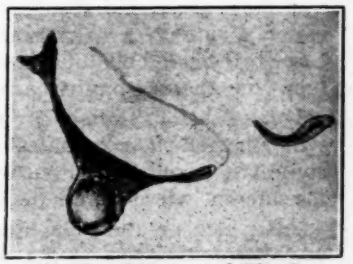


FIG. E.—Diagram of Fig. 9.

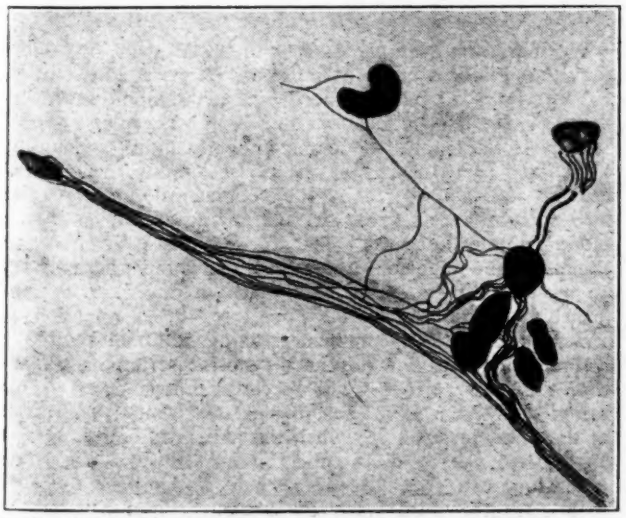


FIG. C.—Diagram made from many photomicrographs like Fig. 4, at different foci, showing nerve fibres terminating round nerve cells inside the rat kidney. (Silver.)

Experimental Data

In an attempt to throw further light on the nature of the cells and their connexions, kidneys have been examined after different methods of renal denervation at

different stages of degeneration. I am grateful to Dr. A. M. Floyer for access to his experimental rat material, from which I have been able to select kidneys at suitable times for studies of degeneration.

Thoraco-lumbar Sympathectomy

This operation was performed on the left side in two rats. The splanchnic nerves—the greater, the lesser, and the least—were cut. The left sympathetic chain was divided about the level of the sixth thoracic vertebra, stripped down to the pelvis, and then removed. Any other fibres which were seen to be going to the kidney were cut.

After periods of three and eight weeks the rats were anaesthetized with ether and both kidneys were exposed.

In some of the thoraco-lumbar sympathectomy cases the denervated kidney and its blood vessels were much larger than the opposite kidney and its blood vessels. This probably resulted from the stimuli arising from opening of the abdomen. In the other cases both kidneys looked about the same. The rats were then deprived of oxygen by obstructing the trachea completely. The intact kidney then contracted to a smaller size and its cortex became mottled and its capsule wrinkled, as was shown by Franklin (1950) in his beautiful technicolour film. The denervated kidney remained unaffected. Thus there was presumptive evidence of the physiological completeness of autonomic denervation in the operated side.

Microscopical Examination.—On examining these denervated kidneys three and eight weeks after operation, nerve bundles were present, though they were much smaller and fewer than in the normal kidney. No thick fibres could be seen. No synaptic formations, as has been described before in the intact material, could be detected. Consequently the nerve ganglia looked less complex (Fig. 12). In number, however, the ganglia appear to correspond with those present in the intact kidney. Some subcapsular nerve fibres can still be found after thoraco-lumbar sympathectomy.

Conclusions

The fact that the very thick fibres can be traced from the hilum to their terminations without interruption and that they give "end feet" to the neighbouring blood vessels may have a special relation to the renal vessels. None of them could be seen after the degeneration following thoraco-lumbar sympathectomy.

During the operation of periarterial (renal pedicle) sympathectomy the operated kidney becomes pale and contracts, which is no doubt due to the stimulation of the efferent nerve fibres.

After degeneration the normal kidney contracts in response to anoxia, as the intact efferent fibres carry vasoconstrictor impulses to the kidney. But the adequately denervated kidney is free from such a higher neuronal control.

The existence of nerve fibres and bundles after denervation may be evidence that nerve cells are present inside the kidney and that these fibres are the processes of such cells. The possibility of incomplete denervation by such operative methods is obvious, and may be partly responsible for the presence of such fibres.

There is a possibility that the variation in thickness and staining reactions of the fibres found in the kidney may be due to difference in the nature of function of the nerve fibres. These may be either sympathetic or parasympathetic, pre- or post-ganglionic fibres, or viscero-afferent fibres.

The glomeruli contain polyhedral cells which appear to send their processes round the capillaries to form spirals. Other polyhedral cells have comma-shaped processes among the glomerular tufts.

The renal tubules receive a rich nerve supply. Intertubular polyhedral cells are present between the adjacent tubules. Both these cells and the glomerular polyhedral cells form groups which presumably have some part to play in the renal function.

Summary

Several varieties of nerve fibres can be found in the kidney. The thickest ones are, on histological grounds, possibly afferent in function. In the kidney undoubted nerve cells can be found along the blood vessels and in the renal papilla and pelvis. In addition, there are widely scattered groups of polyhedral cells which may be nervous in character, as described above.

I am indebted to Professor J. D. Boyd, in whose department this work was done, for his encouraging kindness and advice. Thanks are also due to Dr. M. A. Floyer, of the Medical Unit, the London Hospital, for performing the sympathectomies. I am grateful to Mr. R. Quinton Cox for photographic and technical help, and to Mr. R. F. Birchenough for technical assistance.

REFERENCES

Asfoury, Z. M. El (1950). International Congress of Anatomy, Oxford.
Berkley, H. J. (1893a). *Bull. Johns Hopk. Hosp.*, **4**, 1.
—— (1893b). *J. Path. Bact.*, **1**, 406.
De Muylder, C. (1940). *C.R. Soc. Biol. Paris*, **134**, 114.
—— (1945). Ibid., **139**, 189.
—— (1948). "La contribution du tissu nerveux à la constitution du rein at ses conséquences en pathologie." Université Catholique de Louvain
Franklin, K. J. (1950) *J. Anat.*, **84**, 63.
Harman, P. J., and Davies, H. (1948). *J. comp. Neurol.*, **89**, 225.
Holbrook, M. L. (1883). *Proc. Amer. Soc. Micr.*, **6**, 51.
Kaufmann, J., and Gottlieb, R. (1931). *Amer. J. Physiol.*, **96**, 40.
Kölliker, A. (1893) *S.B. phys.-med. Ges. Würzburg*, **2**, 17.
Mitchell, G. A. G. (1947). *Edinb. med. J.*, **54**, 545.
—— (1950). *Acta anat., Basel*, **10**, 1.
Stöhr, P., jun. (1928). In Möllendorff's *Handbuch der Mikroskopischen Anatomie des Menschen*, **4**, 373. Berlin.

Writing in the *Monthly Bulletin* of the Ministry of Health and the Public Health Laboratory Service (November, vol. 10), Dr. F. O. MacCallum describes the laboratory diagnosis of virus infections of the central nervous system: "(*a*) by isolation of the virus from body fluids, secretions, excretions, or tissues by means of inoculating fertile hens' eggs or animals, or (*b*) by the demonstration of a rising titre of complement-fixing or neutralizing antibodies in the blood in convalescence. The first process is much more expensive and time-consuming than the latter, seldom gives an earlier positive answer, and must in any case be confirmed by serological tests. Therefore, the examination of serum, usually for complement-fixing antibodies, is the method of choice for routine diagnosis; serum neutralization tests are performed in special circumstances. Two samples of serum from each patient are essential, one taken at the onset of illness or when the patient is first seen, and the second usually during the third or fourth week. The laboratory can give little or no help if the patient is first seen after the third week of illness. Virus isolation is usually only attempted in localized outbreaks or in special circumstances."

HAEMOGLOBIN LEVELS BEFORE AND AFTER LABOUR

BY

H. E. MAGEE, D.Sc., M.R.C.P.

AND

E. H. M. MILLIGAN, M.D., D.P.H.

(From the Ministry of Health, Whitehall)

The Medical Research Council in 1943 carried out a survey of haemoglobin levels in Great Britain covering some 16,000 people of different ages and occupations (M.R.C., 1945). From the findings it was inferred that anaemia was probably less prevalent in Great Britain than before the war, but, although the incidence in children and pregnant women was almost certainly less than in the early days of the war, it was considered to be unduly frequent in these groups. The practice of prescribing iron prophylactically as well as therapeutically for expectant mothers was fairly common for some years before 1939, and there is reason to believe that it has increased since the Ministry of Health drew attention to the importance of giving suitable preparations of iron to guard against anaemia occurring in pregnant and nursing mothers (*Med. Offr.* 1943). It was, nevertheless, thought advisable to make, from time to time, occasional small-scale haemoglobin surveys on these vulnerable groups.

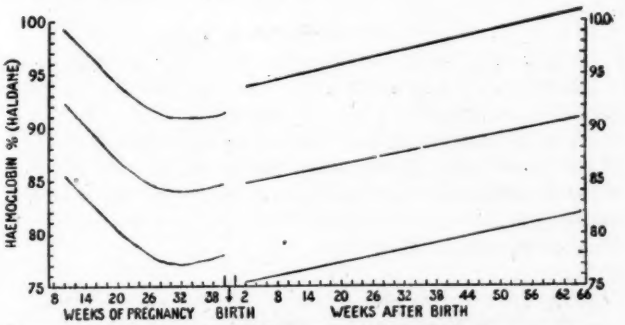
In this paper are reported the results of the statistical analysis of observations made in the Manchester area during the past three to four years on some 2,000 mothers during pregnancy or for a year or more after the birth of their babies. Surveys have also been carried out on schoolchildren, but these are not reported here.

A method for determining haemoglobin suitable for field conditions required some thought. The experience of the M.R.C. survey workers did not inspire confidence in the Haldane instrument, particularly in the hands of persons using it at irregular intervals, as was the case with our observations. Subsequent reports in which the Haldane instrument was compared with others have confirmed the earlier suspicions (Macfarlane, King, *et al.*, 1948). On the advice of Professor King we employed the M.R.C. grey-wedge photometer, using alkaline haematin. The procedure is described fully elsewhere (Adcock *et al.*, 1948). Preliminary accounts of the findings obtained in these surveys have already been published (Magee and Milligan, 1949, 1950). Further statistical analyses of the data obtained during and after pregnancy have brought to light a number of points of interest which we think worthy of more complete record.

Method

The survey was made on women attending the antenatal and child-welfare clinics in and around Manchester. They belonged, for the most part, to the working-class and were, of course, volunteers; there was no selection of any sort. Of all the 2,087 women whose blood was examined, 1,244 were sampled before and 843 after labour. All except 667 were examined clinically, and their nutritional state was assessed by the methods commonly employed by the Ministry's clinicians.

The observations were divided into weekly periods and averaged. From the means so obtained curves were fitted by the method of least squares. These curves are shown in the accompanying Chart. The equations were as follows:



Haemoglobin values of 2,087 women during and after pregnancy. Smooth curves with limits ± 1 S.D.

$$\text{Antenatal Hb} = 100.7 - 1.0x + 0.15x^2 \pm 6.7$$

$$\text{Post-natal Hb} = 84.4 + 0.104x \pm 9.4$$

Where x = time in weeks

The observations were classified into those of women who had been taking iron (1 gr. (65 mg.) t.d.s. of ferrous iron) for three weeks or more before sampling or who had not, and also according to parity.

In the past it has been customary to classify haemoglobin values during and after pregnancy according to where they fell in relation to certain empirically selected levels. The level most often selected was 80% (Haldane), and values falling below this were considered to be too low and were generally regarded as indicative of anaemia. The test was admittedly far from satisfactory, specially during and soon after pregnancy, for it is well known that the haemoglobin in healthy women falls steadily during pregnancy until shortly before labour and rises gradually again after labour. Therefore, in deciding whether a haemoglobin value taken during these periods is or is not satisfactory, account has to be taken of these physiological changes. This was done in the present series of observations, and two curves have been drawn, one standard deviation below and one above the curve of the means. It therefore seems that any values outside these limits are either abnormal or tend to be so.

Results

Mean Haemoglobin Level

The data show a steady decline from nearly 93% at the eighth week of pregnancy to a minimum of just under 81% from the 32nd to the 34th week approximately. Thereafter it rose consistently to nearly 85% at the 39th week. This rise gives the curve a slightly parabolic appearance.

The post-natal curve, on the other hand, is a straight line. It rises from about 85% at the fourth post-natal week to 90.5% at the 65th. The post-natal values are much more irregular than the antenatal, the standard deviation of the former series being 9.4 compared with 6.7 for the antenatal series. It is noteworthy that the level even at the 65th week after labour was still some 2–3% less than the value found at the eighth week of pregnancy. This finding suggests that an early effect of conception is to cause the haemoglobin to rise slightly —a notion which is strengthened by the fact that the mean obtained in 38 healthy nulliparous women of childbearing age employed in the Manchester welfare centres was 88.5%. The M.R.C. Haemoglobin Committee

regarded 98% as the desirable mean for non-pregnant women, but they actually quote means for different groups of between 87.3 and 96%.

Effect of Iron

Of the total of 1,249 women who were classified as taking iron, all but three began taking it before labour and 708 continued to take it for a variable time after labour. The average time for taking iron was 25 weeks; after a year only eight women continued to take it. All women who took iron for three weeks or more were put in the iron group irrespective of the length of time they continued to take it.

TABLE I.—*Effect of Ferrous Iron (1 gr. (65 mg.) t.d.s.) on Haemoglobin During and After Pregnancy*

	Antenatal			Post-natal				
Weeks:	0–13	14–26	27–39	0–13	14–26	27–39	40–52	53+
Iron:								
Hb %	95·1	88·3	84·1	86·3	87·8	87·7	91·0	89·6
S.E.	±1·33	±0·52	±0·35	±0·7	±0·77	±0·88	±1·1	±0·71
No.	17	215	479	189	169	126	86	130
No Iron:								
Hb %	91·5	86·6	80·9	80·5	83·3	84·5	88·2	85·8
S.E.	±0·79	±0·47	±0·64	±1·33	±1·44	—	—	±2·6
No.	92	267	174	44	46	17	9	27
Combined:								
Hb %	92·1	87·4	83·5	85·2	86·8	87·2	90·5	89·0
S.E.	±0·69	±0·37	±0·32	±0·66	±0·66	±0·87	±0·94	±0·58
No.	109	482	653	233	215	143	95	157
Total	1,244			843				
	2,087							

The figures (Table I) show that women having iron had haemoglobin values from 1.7 to 3.6 points higher before labour and from 2.8 to 5.8 higher after labour than women not having iron. It may be that the taking of iron during pregnancy lessened the amount of blood lost at parturition.

The effects of iron medication were more pronounced the longer the iron was taken, as the following figures show :

	No.	Weeks Taking Iron	Hb %
2nd trimester	18	15	90·0
2nd ,, ...	136	5	87·9
3rd ,, ...	42	26	88·5
3rd ,, ...	190	8	82·7

These differences are significant statistically.

The effects of iron taken during pregnancy continued into the post-natal period, but they were not quite so pronounced as when medication was continued into the post-natal period. The following figures demonstrate these differences :

No.	Group	Post-natal Weeks			
		0–13	14–26	27–52	53+
143	No iron (Table I)	80·5	83·3	85·8	85·8
251	Iron for 20·5 weeks before and 9·5 after labour on average	87·3	89·9	92·2	88·8
449	Iron for 22 weeks on average before labour only ..	85·9	86·8	88·0	90·1

The mean values for the three pregnancy trimesters compare very favourably with those obtained in the survey of 1943 (M.R.C., 1945, p. 29). Those for the combined group and especially for the iron group are consistently higher; the M.R.C. values (89, 86, and 82% in the respective trimesters) are almost identical with those for the non-iron group (92, 87, and 81%).

Parity

The figures (Table II) show that child-bearing apparently caused a progressive lowering of the haemoglobin level. The mean difference before labour between primiparae and women who had three or more children

TABLE II.—*Haemoglobin Levels According to Parity*

		Antenatal			Post-natal			
Trimester:		1st	2nd	3rd	1st	2nd	3rd	4th
Parity 1	Hb	93·0	88·0	85·5	87·5	87·0	90·0	91·0
	No.	55	223	285	99	103	115	75
	S.E.	±1·0	±0·5	±0·5	±0·99	±0·83	±0·9	±1·0
Parity 2	Hb	92·0	85·5	83·0	84·5	87·0	87·5	89·5
	No.	32	130	195	79	56	73	45
	S.E.	±1·7	±0·5	±0·57	±0·9	±0·87	±1·15	±1·5
Parity 3	Hb	90·5	86·5	81·5	82·0	87·0	86·5	85·0
	No.	22	129	173	55	56	50	37
	S.E.	±3·7	±0·74	±0·7	±1·5	±1·46	±1·7	±2·1
		109	482	653	233	215	238	157
		1,244			843			
		2,087						

TABLE III.—*Blood Pressure (Systolic) of Women with Low* and High† Hb Levels*

	Low Hb Levels	High Hb Levels
No.	35	38
Mean Hb	70·3% ± 0·55	102% ± 0·86
Mean B.P. (mm. Hg) ..	118 ± 1·7	116 ± 1·4

* Low = 86, 81, or 77% in the respective antenatal trimesters, or 79, 81, 81, or 84% in the respective post-natal trimesters.
† High = 98, 93, or 90% in the respective antenatal trimesters, or 91, 93, 93, 97, or 95% in the respective post-natal trimesters.

varied from 1.5 to 4% ; after labour it varied from 0 to 6%. Iron therapy was not the cause of the higher values in the primiparae, for the proportions of women taking iron in the three parity groups were 88, 83, and 91% respectively.

Haemoglobin and Undernutrition

Of 825 women examined before labour 43 (5.2%) were graded as of fair or poor nutritional state. The mean Hb of the 43 was 82% ± 1.9, and of the 782 of good nutritional state 85 ± 0.3. The small difference of 3% is not significant. In the post-natal period 34 out of 843 women (4%) were graded fair or poor, with a mean Hb of 78 ± 6.7, compared with a mean of 88 ± 0.34 for 809 of good nutritional state. The difference of 10% is significant.

When the antenatal and post-natal periods are taken together, the total graded fair or poor was 77 out of 1,668 (4.6%). This incidence is only slightly above that found in 630 pregnant and nursing women (4%) in various places in England during 1946–7 by the Ministry of Health surveys (Adcock *et al.*, 1948). The incidence of fair or poor nutritional state was higher in women of three or more pregnancies (11%) than in women of the first or second pregnancy (3%).

Women with low Hb were not confined to those graded fair or poor. There were 138 women with low values during pregnancy (that is, below 86, 81, or 77%, or one standard deviation less than the means for the respective trimesters, Table I), but only 43 (31%) of these were graded fair or poor. After labour 104 women had low values (that is, below 79, 81, 81, or 84%, or one

standard deviation less than the means for the respective post-natal trimesters, Table I), but only 34 of them (33%) were graded fair or poor. It is therefore clear from these analyses that low Hb and clinical undernutrition do not always go hand in hand, and there would have been no justification in excluding the values for the fair or poor women from the values on which the curves and Table I are based. The incidence of undernutrition also increased with parity : it was 2.4%, 3.8%, and 12.9% in the first, second, and third parity groups, respectively, in the antenatal period, and 2.8%, 1.9%, and 4% in the postnatal period.

Haemoglobin and Blood Pressure

The blood pressures were taken of women who had haemoglobin levels lower than or higher than the limits set out in Table III—that is, more than a standard deviation below or above the means in Table I. It is clear from the figures in Table III that there is no difference between the mean blood pressure of women with low and of those with high Hb.

Discussion

The general trend of the Hb level in pregnancy is well known ; the fact that the lowest level reached is not immediately before labour but some eight weeks previous to this is not, however, so well known. This had been brought out previously by the work of Boycott (1936), Fullerton (1936), M.R.C. (1945, p. 30), and Mull and Bill (1945). The changes in Hb are in harmony with the increases in the blood and plasma volumes and with the declines in the concentration of other constituents, such as urea, calcium, and potassium, which have been observed by several authors—for example, Dieckmann and Wegner (1934), Mull and Bill (1945), and McLennan and Thouin (1948). Caton, Roby, Reid, and Gibson (1949) have shown that shortly before the onset of labour there is a diminution in plasma volume of about 25% of the volume during pregnancy. There can be no doubt that the changes in the concentration of the blood constituents are brought about mainly by the corresponding changes in blood volume, even though McLennan and Thouin found that the total Hb in the body actually increased by some 20% during pregnancy.

These changes, however, merely describe but do not explain the phenomenon. For an explanation we should want to know the cause and the significance of the hydraemia, but the evidence available and theoretical considerations do not provide an answer. Nevertheless, the establishment of the facts about the changes in the blood constituents in pregnancy is useful in so far as it enables one to judge the normality of Hb determinations made during pregnancy. The curves shown in the Chart may be found useful in this way.

The post-natal curve, which is a straight line, has three noteworthy features : (*a*) a very slow rise ; (*b*) the irregularity of the values (the S.D. is 9.4 compared with 6.7 for the antenatal values) : and (*c*) the highest point reached, 90.5, is still, at 65 weeks after labour, two points less than the beginning of the pregnancy curve (see Chart). The reasons for (*a*) and (*b*) are not apparent from theoretical considerations or from our own or any other experimental evidence available. In regard to (*c*) it should be noted that the mean value for 38 non-parous women of child-bearing age in the Manchester clinics was 88.5%, or two points below the final value on the post-natal curve. We are therefore inclined to the view that 90.5% is substantially the normal value for non-parous and non-pregnant women and that an early effect of pregnancy is to cause a slight rise in Hb.

Hb levels after pregnancy seem to have been litt'e studied. Fullerton's (1936) observations are the only attempt at systematic study we know of ; his values are at a generally lower level than ours, rising gradually from 74% just after labour to 85% at 12 months. This is approximately at the same level as for our own non-iron group, but some 3–4% below the combined iron–non-iron groups. It is probable that the disappearance of hydraemia plays only a minor part in the recovery of the Hb in the post-natal period, because Caton *et al.* (1949) found that the plasma volume had returned to normal non-pregnant values 30 days after delivery.

The influence of parity is brought out clearly by the figures in Table II. The Hb was consistently lower with successive pregnancies both after and before labour. Iron can be dismissed as a factor, since the proportions taking iron in the three parity groups were 88, 83, and 91%. Age can also be ruled out ; for, as Wintrobe (1946) points out from an extensive review of the literature, the Hb of non-parous women remains constant between about 20 and 65 years of age. The same effect of successive pregnancies was shown in the M.R.C. survey (M.R.C., 1945, p. 29), but the decline was less consistent.

The taking of iron consistently raised the Hb level, especially in the post-natal period, and the higher level was maintained for several months on the average after iron medication ceased. The return of the blood volume to the non-pregnant level shortly after the puerperium is not concerned, since the higher Hb was observed more than a year after labour in women who had taken no iron at all in the post-natal period.

The great bulk of the women, whether taking iron or not, were perfectly healthy and had no complaints, which raises the question whether a Hb level raised by iron therapy is in itself an advantage. To answer this question more precise clinical inquiries than we were able to make would be necessary.

Summary

The Hb levels of 2,087 unselected women attending welfare clinics were determined by the grey-wedge method at different times during pregnancy and after birth. The values were averaged in weekly periods, and curves were fitted by the method of least squares. It is suggested that these curves may be found useful to assess the normality of Hb values during and after pregnancy.

The antenatal curve agrees with previous observations and shows a rapid decline from 93% (Haldane) at the 8th week to a minimum of about 81% between the 32nd and 34th weeks, and then a rise to nearly 85% at the 39th week. Comparison of the curve with the levels found in healthy non-parous women of child-bearing age suggests that conception causes the Hb to rise in the early weeks of pregnancy.

The post-natal curve is a straight line, rising from 85% at the 4th to 90.5% at the 65th post-natal week. The values showed more variability than the antenatal ones.

The women who were taking or had recently taken iron (usually 1 gr. (65 mg.) of ferrous iron t.d.s.) had levels 1.7–3.6 points higher before labour and 2.8–5.8 points higher after labour than women who did not have iron. The longer iron was taken the more effective it was, and the effects persisted into the post-natal period even when nearly all women had ceased taking it.

Repeated pregnancies progressively lowered the Hb level.

The mean Hb level of 43 out of 825 women clinically graded before labour as of fair or poor nutritional state was slightly but not significantly lower than the mean for 782 women of good nutritional state. The mean for 34 out of 843 women graded fair or poor after labour was significantly lower than that of the remaining 809 women graded good. Only about one-third of women with values more than one S.D. below the mean were found of fair or poor nutritional state; the remaining two-thirds appeared to be quite healthy.

The systolic blood pressure of women with low Hb did not differ from those with high Hb.

We are much indebted and wish to record our thanks to Drs. C. Metcalfe Brown and J. L. Burn for permission to conduct the surveys in their clinics and for much courtesy and help, and to Mr. W. H. Hammond for statistical advice and help.

REFERENCES

Adcock, E. W., Magee, H. E., and Milligan, E. H. M. (1948). *Mon. Bull. Minist. Hlth, Lond.*, **7**, 165.
Boycott, J. A. (1936). *Lancet*, **1**, 1165.
Caton, W. L., Roby, C. C., Reid, D. E., and Gibson, J. G. (1949). *Amer. J. Obstet. Gynec.*, **57**, 471.
Dieckmann, W. J., and Wegner, C. H. (1934). *Arch. intern. Med.*, **53**, 71, 188, and 345.
Fullerton, H. W. (1936). *British Medical Journal*, **2**, 577.
Macfarlane, R. G., King, E. J., Wootton, I. D. P., and Gilchrist, M. (1948). *Lancet*, **1**, 282.
McLennan, C. E., and Thouin, L. G. (1948). *Amer. J. Obstet. Gynec.*, **55**, 189.
Magee, H. E., and Milligan, E. H. M. (1949). *Brit. J. Nutrit.*, **3**, xii.
—— —— (1950). Ibid., **4**, xv.
Medical Officer (1943). **69**, 147.
Medical Research Council (1945). Spec. Rep. No. 252. H.M.S.O., London.
Mull, J. W., and Bill, A. H. (1945). *J. Lab. clin. Med.*, **30**, 458.
Wintrobe, M. W. (1946). *Clinical Haematology*, p. 77. Kimpton, London.

Leprosy was widespread in Scotland from the eleventh to the fifteenth centuries, but in 1530 the magistrates of Edinburgh decreed that no leper might enter the city, and throughout the country they had to sound clappers when begging; this segregation undoubtedly did much to banish the disease (*Scientific Survey of South-eastern Scotland*, British Association for the Advancement of Science, 1951, p. 79). Until the fourteenth century Scotland was almost free of the plague, and it then appeared following a raid across the border, destroying one-third of the population. The first attempt at the control of the disease was the Rule of Pestilence, an Act passed over 100 years later. The measures adopted by local authorities were intended to prevent the spread of the disease rather than to care for those infected, and the main reason for the disappearance of the plague was not the advance of medicine but the fact that the vector, the black rat, was replaced by the brown or sewer rat in the seventeenth and eighteenth centuries. Early in the sixteenth century the town council of the City of Edinburgh began to make efforts to clean the streets, and one year the Provost had them cleaned at his own expense and used the refuse to manure his private estate. Smallpox was very prevalent, and until about 1750 accounted for 10% of all deaths in the city; the College of Physicians of Edinburgh pronounced the practice of inoculation to be highly salutary to the human race. It was not until the great outbreaks of cholera a century later that boards of health were set up in many towns and villages to protect the communities, and the streets were cleaned, hospitals equipped, and infected areas fumigated. But as soon as the state of emergency was over these measures were relaxed. The first medical officer of health was appointed in 1862 after public attention had forcibly been drawn to the problem of overcrowding and insanitary conditions by the collapse of a house in Edinburgh which killed 35 people.

DIFFUSE ARTERITIS OF UNKNOWN ORIGIN ACCOMPANIED BY EOSINOPHILIA

BY

K. W. WALTON, M.D.
Lecturer in Pathology, Birmingham University

AND

D. W. ASHBY, M.D., M.R.C.P.
Physician, Gateshead Group of Hospitals

There is a growing body of evidence that morphologically similar changes may occur in the arteries in a number of conditions presenting widely differing clinical characters. These arterial changes may be either acute or chronic, but are all of an inflammatory granulomatous type. The whole thickness of the vessel wall is involved and the inflammatory exudate often contains a proportion of eosinophil leucocytes. An eosinophilia of the peripheral blood may or may not form part of the clinical picture.

When the arteritis is the most prominent component of the disease, and especially when it is acute and confined mainly to the visceral vessels, the condition is usually labelled polyarteritis nodosa. When it is subacute or chronic and involving the arteries arising from the aorta proximal to their points of entry into the viscera, the generalized form of temporal or giant-cell arteritis (Harrison, 1948) is sometimes diagnosed. Occasionally the striking feature is the intensity of the eosinophilia, as a result of which the case is now and then initially misdiagnosed as eosinophilic leukaemia (Blackburn, 1950).

The histological similarity between the vascular and connective-tissue lesions of polyarteritis nodosa and those of lupus erythematosus disseminatus, the generalized form of scleroderma, dermatomyositis, rheumatic polyarthritis, and certain other ill-defined conditions associated with transient eosinophilic infiltration of the lungs, has been noted by many authors (e.g., Jaeger, 1932; Roessle, 1933; Banks, 1941; Bergstrand, 1946). This resemblance has occasioned much speculation about whether the lesions have a common aetiological origin in being hypersensitive or allergic reactions. Klemperer *et al.* (1942), while admitting that these conditions have a common basis in being diffuse collagen diseases with similar vascular changes, deplore, as an oversimplification, the attempt to ascribe to them all the same causal origin.

Apart from the clinical entities mentioned, there are cases like that described by Lumb (1950) with references to others in the literature which show similar vascular and collagenous lesions to those mentioned above, but which evade satisfactory classification. We have thought it might be of interest to report another such case of diffuse arteritis in which the clinical picture had features in common with polyarteritis nodosa, temporal arteritis, eosinophilic leukaemia, and the clinical syndrome described by Lewi (1949) and ascribed by him to hypersensitivity to chemotherapeutic drugs. Our case did not correspond entirely with any one of these conditions, and though we suspected on general grounds that it might be allergic in origin we were unable to obtain any direct proof of this.

Case Report

On February 8, 1950, a gas-meter tester aged 56 was admitted to hospital. On January 14 he had had an attack of "gastro-enteritis" with diarrhoea, vomiting, and slight fever. After five days a rash developed, first on the extensor aspects of the elbows and forearms, spreading to the front of the chest, abdomen, and inner aspects of the thighs and legs. The rash began as a diffuse redness and became eczematous and itchy. At the beginning of February there were spasmodic and painful attacks of transient digital angiospasm, following which the four fingers and nails of each hand became dusky and cold, but the thumbs escaped. On February 6 and 7 there were transient attacks of visual disturbance which he described as resembling a shower of sparks in front of his left eye. These attacks lasted from half a minute to three minutes and did not recur. There was no history of allergic complaints or of drug sensitivity. None of his family had suffered from allergy.

FIG. 1.—Showing nature of skin rash on February 24, 1950. Note also prominence of thrombosed right temporal artery.

On examination his temperature was 100° F. (37.8° C.). He had a rash involving the skin of the arms, legs, and trunk. This was in the first instance an erythroderma, but there was a recently developed papulo-vesicular eruption on the outer aspects of the forearms which was intensely itchy. A purplish discoloration and coldness of the fingers of both hands were present (see Fig. 2), the middle finger of the left hand being most severely involved. The thumbs and the toes escaped. The radial pulse could not be felt at either wrist beyond a point 1 in. (2.5 cm.) proximal to the wrist-joint. The temporal artery on the right side was visibly thickened, did not pulsate, and appeared to contain clot in its anterior division (see Fig. 1). Neither dorsalis pedis pulse was palpable, but there was no cyanosis of the toes. The posterior tibial pulses were easily felt. Examination of

FIG. 2.—Showing gangrene of fingers and skin rash on back of forearms on March 9, 1950.

the heart revealed no abnormality. His blood pressure was 130/75. The lymph nodes of the axillae, groins, and femoral groups were enlarged, rubbery, discrete, and non-tender. The spleen was palpable at a point two fingerbreadths beneath the left costal margin.

Haematology.—On February 8 the red cells numbered 4,820,000 per c.mm. and the white cells 27,700 per c.mm. (Fig. 3), 70% of these being eosinophils, composed as follows: 13,919 mature eosinophils, 1,593 eosinophil band forms, and 3,809 "ruptured" eosinophils. The stained films were reported on by Dr. A. L. P. Peeney as follows: "The granules in the eosinophils were rather more golden in colour than in typical eosinophils. A small number showed 'multi-coloured granulation,' suggesting that nuclear development had occurred more quickly than granule maturation. Dissociation of nuclear and cytoplasmic maturation in allergic eosinophilia has been noted by several authors. Cytoplasmic vacuolation was present in many cells, and in a small number granules were conspicuously few. Many of the eosinophils were rather distorted in shape and there was an appreciable number of broken forms." Professor J. R. Squire showed that the eosinophils were normally motile.

Sternal puncture on February 10 showed 8.25% eosinophil myelocytes, 6.75% eosinophil band forms, and 19.25% segmented eosinophils. Immature eosinophils were not conspicuous. Electrocardiograms and *x*-ray films of chest revealed no abnormality. The urine contained no albumin, and the blood urea was 38 mg. per 100 ml. The serum W.R. was negative. Examination of the stools revealed no parasites or ova.

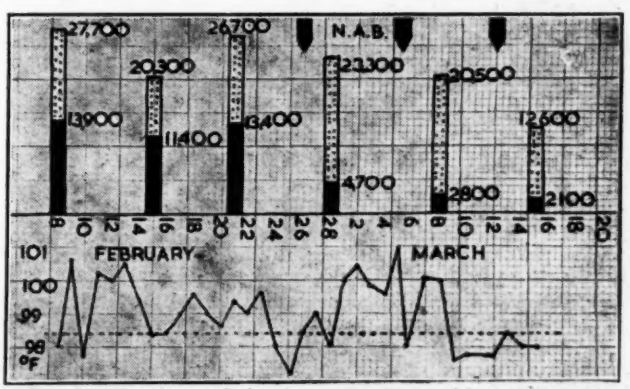


FIG. 3.—Showing variation in temperature and leucocyte count. Black portion of column shows eosinophil count (mature forms only).

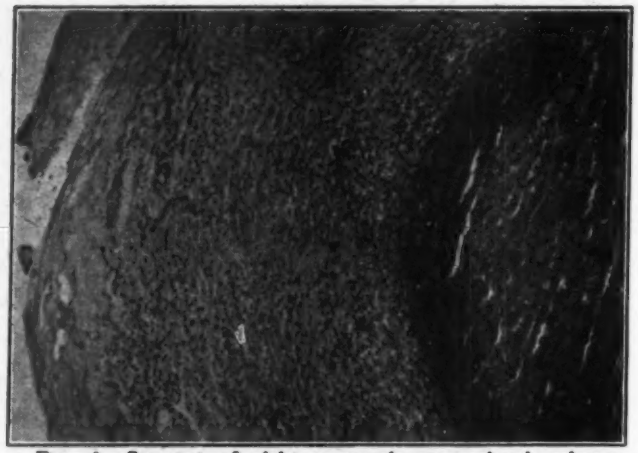


FIG. 4.—Segment of right temporal artery showing lumen occupied by recently formed thrombus and diffuse inflammatory change in arterial wall. (H. and E. ×90.)

Pathology of Material Taken for Biopsy

Skin.—The section showed oedema of the superficial dermis and the epidermis. In one area the keratinized layer of the epidermis was lifted by the formation of a vesicle. The dermis showed scattered cellular infiltrations by lymphocytes, plasma cells, and occasional eosinophils, with a tendency for aggregation of these cells to occur around the small vessels.

Muscle.—A biopsy taken from the deltoid showed separation of the muscle fibres and a slight diffuse infiltration with inflammatory cells, including a large proportion of eosinophils. In two areas these cells were concentrated around two blood vessels, less than 100 μ in diameter, in a manner suggestive of polyarteritis nodosa, but no larger arteries were included in the biopsy material to allow study of the changes within the vascular wall.

Axillary Lymph Node.—The node showed the normal age changes of fatty infiltration of the hilum and medulla. The architecture of the lymphoid tissue was well preserved and the capsule intact. The lymphoid follicles showed hyperplasia with active "germinal centres." The peripheral and medullary sinuses contained numbers of eosinophil leucocytes.

Dorsalis Pedis Artery.—The vessel showed considerable patchy inflammatory thickening of the intima. In the subendothelial tissue organizing fibrin, histiocytes, and a moderate number of eosinophils were seen. The media showed marked fibrosis and a chronic inflammatory granulomatous process extending into the adventitia. The granulomatous tissue consisted mainly of histiocytes, but here and there many eosinophils could be seen. Sections cut at various levels did not show giant-cell formation.

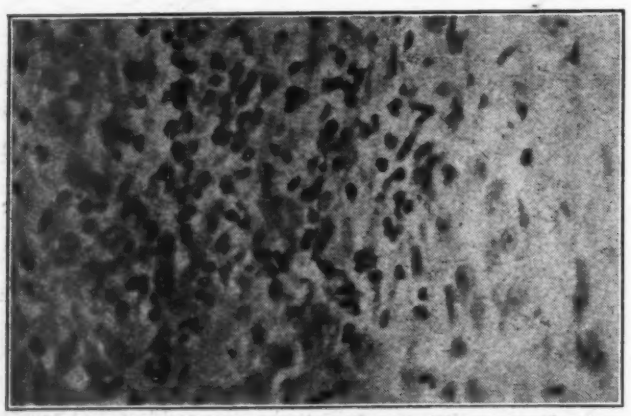


FIG. 5.—High-power view of media of right temporal artery showing infiltration by acute and chronic inflammatory cells, including a few eosinophils. (H. and E. ×400.)

Temporal Artery.—The artery contained a recently formed thrombus (Fig. 4) in which organization was just beginning. All coats of the arterial wall showed a marked infiltration by acute and chronic inflammatory cells, including many eosinophils (Fig. 5). The media showed diffuse fibrosis, and fragmentation and almost complete disappearance of the elastic laminae. A chronic inflammatory granulomatous process was visible in the outer layers of the media and in the adventitia. Sections cut at various levels showed an occasional giant cell present in the neighbourhood of surviving fragments of elastic tissue (Fig. 6). The vasa vasorum showed a perivascular cuffing by inflammatory cells.

Amputated Right Middle Finger.—A section was made through the middle of the proximal phalanx. This showed necrosis of all the soft tissues with widespread infiltration from the ulcerating skin surface by acute and chronic inflammatory cells. The digital vessels were thrombosed, and there was a marked inflammatory change in their walls and in the perivascular tissues, but it was not possible to be certain that this was a process separate and apart from the necrosis and inflammatory change proceeding in the other soft tissues.

Comment on the Findings

The changes in the skin, muscle, and lymph node suggested an acute exudative process, possibly of allergic origin, in view of the universal occurrence of increased numbers of eosinophils. The changes in the lymph node

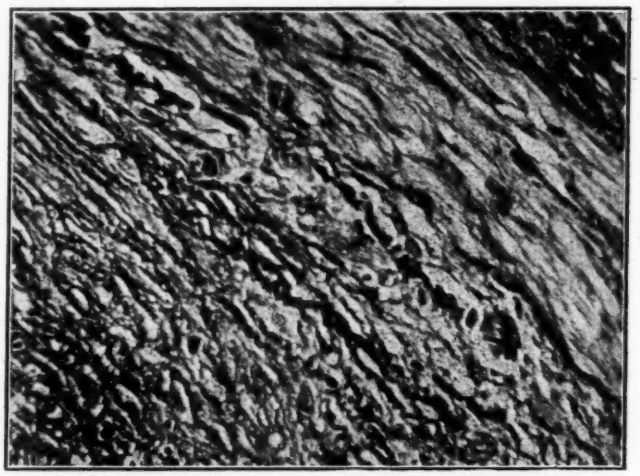


FIG. 6.—Right temporal artery. Media lower left. Adventitia upper right. External elastic lamina from top left to bottom right. Note disruption of external elastic lamina and presence of giant cells in apposition to fragments of elastic tissue in external elastic lamina. (Verhoeff and van Gieson. ×270.)

were particularly interesting, as they were probably secondary to the widespread skin disease and could perhaps be regarded as an early stage of the lymphadenopathy described by Pautrier and Woringer (1937) in more chronic cases of exfoliative dermatitis.

The arterial changes resembled those seen in temporal arteritis and in polyarteritis nodosa, the presence of increased numbers of eosinophils and the scantiness of giant cells making the latter diagnosis more probable. If the changes in the radial arteries (which were not biopsied) were of a similar character to those in the temporal and dorsalis pedis, then the distribution of the arterial changes was unusual for either of the preceding conditions. The generalized form of temporal arteritis is usually stated to affect the elastic and larger muscular arteries arising direct from the aorta and proximal to their points of entry into the viscera, while polyarteritis is usually said to affect the small muscular arteries in the viscera (Harrison, 1948). The distribution, in fact, resembled in some respects that of thromboangiitis obliterans, but the histological character of the lesion showed necrosis of the media, a lesion not characteristic of this disease.

There appeared to be good reason, in short, for regarding the vascular lesions as of a non-specific character, possibly forming part of an intense generalized allergic reaction.

Treatment and Progress

Vascular Lesions.—Digital gangrene was treated by keeping the limbs cold and administering in turn "padutin," alpha-tocopherol, D.C.A., and intravenous vitamin C and imidazoline hydrochloride ("priscol"). At first a progressive darkening of the fingers occurred and lines of separation developed. The left middle finger became ulcerated, and on March 27 it became necessary to amputate it. On April 23 there was a little blackening at the base of the thumb-nails, and the left big toe became cold and dusky, but gangrene did not supervene. A nodule appeared on the right upper arm on May 14; this was at first thought to be a new polyarteritic lesion, but with its extension it was found to be a venous thrombosis. At the time of discharge on June 2 the patient had been taking priscol for one month and no extension of gangrene had occurred. Furthermore, the radial pulses were palpable throughout their extent.

Glands.—The lymph nodes and spleen remained unchanged throughout most of the course, but tended to recede during the last month of treatment.

Skin.—Initially there was a diffuse reddening and thickening of the skin with some vesiculation on the outer aspects of the forearms. This spread to involve an extensive area of the front of the trunk and neck, becoming eczematous. Thence it involved a large "V" in the neck and intermammary region (see Fig. 1). The rash was treated with antihistamine drugs—mepyramine hydrogen maleate ("anthisan"), 100 mg. twice a day, and promethazine hydrochloride ("phenergan"), 25 mg. at night. Various local applications of calamine and ichthyol and Lassar's paste were used from time to time. The itching remained severe throughout the course of antihistamine compounds. At the end of April the rash began to clear on the face, and during May he was able to shave normally. At the time of discharge the rash was still present on the neck and extensor surfaces of the arms, but it was then dry and non-irritating, and had improved out of all recognition.

Changes in the Peripheral Blood.—These are listed in Table I. The intravenous N.A.B. was given empirically

TABLE I

Date	Total No. of White Cells	Eosinophils		Date Intravenous N.A.B 0·45 g. Given
		Total	Percentage	
8/2/50	27,700	13,919*	50·25	
15/2/50	20,300	11,429	56·3	
21/2/50	26,700	13,400	50·2	27/2/50
1/3/50	23,300	4,730	20·3	
				5/3/50
8/3/50	20,500	2,800	13·6	12/3/50
15/3/50	12,600	2,104	16·7	
22/3/50	17,700	1,062	6	
30/3/50	19,500	4,231	21·7	
5/4/50	18,300	6,460	35·3	
11/4/50	21,900	6,132	28	
19/4/50	19,100	3,572	18·7	
27/4/50	18,200	2,785	15·3	
3/5/50	14,800	3,063	20·7	
12/5/50	16,400	3,559	21·7	
16/5/50	23,900	8,293	34·7	
25/5/50	16,900	6,135	36·3	

* Mature eosinophils only. 1,593 band forms and 3,809 ruptured eosinophils also present.

in view of the response of tropical eosinophilia to this drug. There was a fall in the number of eosinophils coinciding with its administration.

Renal and Cardiac Involvement.—Throughout the course there was no evidence of cardiac involvement as measured by clinical examination and serial electrocardiography. The blood pressure remained normal. Urine samples showed no evidence of blood or casts. The blood urea, with two unexplained exceptions, remained normal (Table II).

TABLE II

Date	Blood Urea	Plasma Proteins	
		Albumin	Globulin
13/2/50	38 mg. per 100 ml.		
20/3/50	79 " " " "		
29/3/50	35 " " " "	3·8 g.	2·6 g.
3/4/50	43 " " " "		
13/4/50	206 " " " "		
19/4/50	30 " " " "	3·8 g.	2·5 g.
4/5/50	30 " " " "		
25/5/50	27 " " " "		

Figs. 7 and 8 show the state of the hands and the general appearance of the patient on June 1. He was discharged on June 2 with considerable improvement of his rash, the spleen diminished in size, and the glands, particularly those in the right axilla, somewhat smaller.

FIG. 7.—Showing state of hands on June 1, 1950.

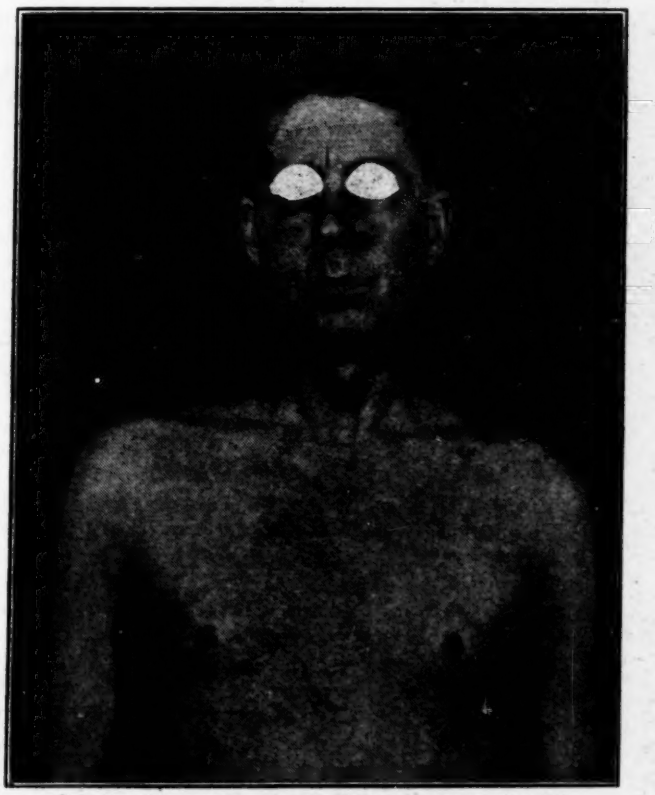


FIG. 8.—General appearance of patient on June 1, 1950.

Follow-up Examination

At a follow-up on August 21 the pulses had returned to his posterior tibial and dorsalis pedis arteries, there was no evidence of gangrene of the toes, and the dry gangrene of the fingers was showing lines of separation. The patient had continued on priscol for only three weeks, after which he had stopped taking it, thinking that it aggravated the swelling of his fingers. The thickened temporal artery was no longer visible. The spleen was not palpable, and the glands were smaller in size. The rash had greatly improved, being present only on his trunk and arms in a dry, branny, non-irritating form. A blood count on August 14 showed 16,700 white cells, of which 21% (3,507) were eosinophils.

The patient was readmitted on September 18, and amputation of his fingers was carried out on the 23rd. The distal phalanges of all fingers, together with the distal end of the middle phalanx of the second and third fingers, were removed from the right hand, and two distal phalanges from the left hand. The improvement in his general health was remarkable, and it was considered not unlikely that he would be able to resume work despite his deformed hands.

Blood urea on September 26 was 42 mg. A modified Calvert's test displayed good renal function. A white-cell count on September 16 showed 8,400 polymorphs, of which 10.3% (865) were eosinophils.

Discussion

The objective evidence of disease found in this patient suggested an underlying pathology of widespread arteritis, but the clinical picture did not correspond in all particulars with the types of arteritis described as clinical entities.

Relationship to Polyarteritis Nodosa

The protean symptomatology and course of polyarteritis nodosa have been sufficiently emphasized by Grant (1940), so that cases presenting with almost any combination of symptoms and signs tend to be so diagnosed provided there is evidence of widespread inflammatory arterial lesions. It is stressed by most authors, however (Grant, 1940; Logue and Mullins, 1946), that polyarteritis nodosa mainly affects the visceral vessels. Harris *et al.* (1939) give the relative frequency of involvement of the viscera as follows; kidneys 87%, heart 84%, liver 71%, spleen 31%, lungs 25%. In the present case clinical investigations failed to reveal any evidence of renal, cardiac, or pulmonary involvement. Rashes of many kinds have been described as occurring in association with polyarteritis (Grant, 1940), but we have been unable to find a record of the occurrence of erythroderma progressing to exfoliative dermatitis as in our case, though a case of exfoliative dermatitis ascribed to hypersensitivity to diphenylhydantoin sodium was shown at necropsy to have periarteritic lesions (Van Wyk and Hoffmann, 1948).

Relationship to Temporal or Cranial Arteritis

This condition was described by Horton and Magath (1937) and was thought to affect the cranial arteries alone. Cases of generalized arterial involvement have been described by Cooke *et al.* (1946). In our case the temporal artery was affected, but the recorded cases of cranial arteritis have not shown evidence of some of the other features present in that case. Thus eosinophilia is uncommon and when present is of minor degree (Kilbourne and Wolff, 1946), skin rashes are usually absent, and the disease is habitually mild in its course and self-limited in duration. Harrison (1948) lists the recorded occurrence of the lesions in temporal or giant-cell arteritis in other vessels as follows: aorta, 9 times; carotid arteries, 6 times; iliac arteries, 4 times; mesenteric and subclavian arteries, 3 times; innominate and femoral arteries, twice; pulmonary, coronary, coeliac, renal, radial, and retinal arteries, once each. Involvement of the dorsalis pedis arteries has not been described.

Relationship to Eosinophilic Leukaemia

Had it not been for the lesions in the radial and temporal arteries, the eosinophilic leukaemoid blood picture and the enlarged glands and spleen might have inclined us to the diagnosis of eosinophilic leukaemia. It is commonly stated by haematologists (Downey, 1938; Wintrobe, 1946; Whitby and Britton, 1950) that eosinophilic leukaemia does not behave as a typical leukaemia, the cells of the peripheral blood being unduly mature, the infiltration of the organs being of a passive nature, and the disease being sometimes benign and self-limited in its course. Indeed, Piney (1949) questioned whether eosinophilic leukaemia exists. It is tempting to suggest that at least some of the cases described under this heading may be cases similar to our own in which polyarteritic lesions are minimal or absent. Blackburn (1950) has described a case of polyarteritis nodosa which, but for the necropsy, would have been considered to be eosinophilic leukaemia., Engbaek *et al.* (1942), reviewing 13 reported cases of eosinophilic leukaemia, found arterial involvement in 5; and Svanberg (1944), reviewing 14 cases, believed that a diagnosis of polyarteritis nodosa had been overlooked in one or possibly two cases. In our case, in spite of the high peripheral eosinophilia, the sternal marrow showed neither the cellularity nor the shift towards immaturity of the marrow elements which would justify a diagnosis of leukaemia. The morphological changes in the blood films were such as are found in stress eosinophilia due to any cause.

Relationship to Arteritis Ascribed to Hypersensitivity

Many authors subscribe to the view that hypersensitivity may be responsible for the variety of arteritis under discussion. For example, Hall (1948), under the collective term "necrotizing angiitis," has grouped together the vascular lesions of polyarteritis nodosa, rheumatic polyarthritis, temporal arteritis, lupus erythematosus disseminatus, and malignant nephrosclerosis, ascribing to the whole group an allergic basis. Of this group, most attention has been concentrated upon polyarteritis nodosa, and there has been much support for the view, first expressed by Gruber (1925), that this condition might arise as a general hypersensitive reaction to some foreign agent, such as serum. The experiments of Rich (1942) and of Rich and Gregory (1943) are often quoted in support of this hypothesis. These authors noted the development of polyarteritic lesions in patients with serum sickness or following sensitization to sulphonamides, and reported that similar lesions could be reproduced in experimental animals sensitized to the same antigens. Similar results were obtained by Hopps and Wissler (1946), but Alston *et al.* (1947) were unable to reproduce Rich's results.

Lewi (1949) has described widespread arterial disease resembling polyarteritis nodosa as one component of a number of allegedly allergic manifestations complicating sulphonamide therapy, and has grouped these together as "the secondary syndrome of chemotherapy." This condition is well illustrated by a case described by Suchett-Kaye (1950). This author reported a patient in

whom, following sensitization to and subsequent administration of sulphonamides, there occurred (i) sensitization dermatitis, (ii) toxic erythema, (iii) dyspnoea resembling asthma, (iv) migraine, and (v) polyarteritis nodosa. Our case presented a somewhat similar train of events providing presumptive evidence of an allergic basis, but questioning failed to elicit any history of exposure to sulphonamides or any personal or family history of allergy.

The chemical compounds, other than sulphonamides, sensitivity to which has been held responsible for polyarteritis nodosa are : desoxycorticosterone acetate (Selye *et al.*, 1944), thiourea (Gibson and Quinlan, 1945), organic arsenicals (Miller and Nelson, 1945), and iodine (Rich, 1945). In our case there was no history of exposure to any of these drugs. The marked eosinophilia which was present in our case could not be regarded as more than suggestive evidence of allergy, as it has been shown to be an inconstant concomitant of at least one form of proved hypersensitivity to drugs (e.g., Cruickshank and Squire, 1949), while it may occur occasionally in conditions demonstrably without allergic basis (Bickel, 1950).

Accordingly, we have regarded the condition described above as a diffuse arteritis, resembling other more clearly defined varieties of granulomatous arteritis, but have considered the likelihood of its having been allergic in origin as unproved.

Summary

A case is described which showed the progressive development of diarrhoea and vomiting, acute erythroderma going on to exfoliative dermatitis, Raynaud's symptom-complex leading to gangrene of the fingers, transient visual disturbances, enlargement of spleen and lymph nodes, pyrexia and leucocytosis with eosinophilia, thrombosis of temporal and radial arteries, and remarkable and unexpected recovery.

Biopsies from various sites showed evidence of widespread inflammatory arteritis with eosinophilic infiltration of the tissues and viscera.

The relationship of this case to various other conditions showing similar histological changes and of supposedly allergic origin is discussed.

Our grateful thanks are due to Dr. Ernest Bulmer for permission to record the case admitted under his care, to Dr. A. L. P. Peeney and Mr. Garfield Thomas for their help with the pathological investigations, and to Professor J. R. Squire and Professor J. W. Orr for their advice and criticism in the preparation of the manuscript. We are indebted to Mr. T. F. Dee and Mr. F. Bradley for the photographs and photomicrographs.

REFERENCES

Alston, J. M., Cheng, K. K., and Short, R. H. D. (1947). *J. Path. Bact.*, **59**, 490.
Banks, B. M. (1941). *New Engl. J. Med.*, **225**, 433.
Bergstrand, H. (1946). *J. Path. Bact.*, **58**, 399.
Bickel, G. (1950). *Acta allerg., Kbh.*, Suppl. 1, 57.
Blackburn, C. R. (1950). *Amer. J. med. Sci.*, **220**, 313.
Cooke, W. T., Cloake, P. C. P., Govan, A. T. D., and Colbeck, J. C. (1946). *Quart. J. Med.*, **15**, 47.
Cruickshank, C. N. D., and Squire, J. R. (1949). *Brit. J. industr. Med.*, **6**, 164.
Downey, H. (1938). *Handbook of Haematology*, 1st ed., 4, 2949. Hamish Hamilton, London.
Engbaek, H. C., Heerup, L., and Thomsen, S. (1942). *Nord. Med.*, **14**, 1535.
Gibson, P. C., and Quinlan, J. T. (1945). *Lancet*, **2**, 108.
Grant, R. T. (1940). *Clin. Sci.*, **4**, 245.
Gruber, G. B. (1925). *Virchows Arch.*, **258**, 441.
Hall, E. M. (1948). In Anderson's *Pathology*, 1st ed., p. 584. Kimpton, London.
Harris, W. A., Lynch, G. W., and O'Hare, J. P. (1939). *Arch. intern. Med.*, **63**, 1163.
Harrison, C. V. (1948). *J. clin. Path.*, **1**, 197.
Hopps, H. C., and Wissler, R. W. (1946). *J. Lab. clin. Med.*, **31**, 939.
Horton, B. T., and Magath, T. B. (1937). *Proc. Mayo Clin.*, **12**, 548.
Jaeger, E. (1932). *Virchows Arch.*, **284**, 526.
Kilbourne, E. D., and Wolff, H. G. (1946). *Ann. intern. Med.*, **24**, 1.
Klemperer, P., Pollack, A. D., and Baehr, G. (1942). *J. Amer. med. Ass.*, **119**, 331.
Lewi, S. (1949). *Ann. Méd.*, **50**, 295.
Logue, R. B., and Mullins, F. (1946). *Ann. intern. Med.*, **24**, 11.
Lumb, G. (1950). *British Medical Journal*, **2**, 645.
Miller, H. G., and Nelson, M. G. (1945). *Lancet*, **2**, 200.
Pautrier, L. M., and Woringer, F. (1937). *Ann. Derm. Syph., Paris*, **8**, 257.
Piney, A. (1949). *Rev. Hémat.*, **4**, 3.
Rich, A. R. (1942). *Bull. Johns Hopk. Hosp.*, **71**, 123, 375.
—— (1945). Ibid., **77**, 43.
—— and Gregory, J. E. (1943). Ibid., **72**, 65.
Roessle, R. (1933). *Virchows Arch.*, **288**, 780.
Selye, H., Beland, E., and Sylvester, O. (1944). *Exp. Med. Surg.*, **2**, 224.
Suchett-Kaye, A. I. (1950). *British Medical Journal*, **1**, 704.
Svanberg, T. (1944). *Nord. Med.*, **22**, 948.
Van Wyk, J. J., and Hoffmann, C. R. (1948). *Arch. intern. Med.*, **81**, 605.
Whitby, L. E. H., and Britton, C. J. C. (1950). *Disorders of the Blood*, 6th ed., p. 486. Churchill, London.
Wintrobe, M. W. (1946). *Clinical Haematology*, 2nd ed., p. 703. Kimpton, London.

MULTIPLE ARGENTAFFINOMATA OF ILEUM REVEALED BY SECONDARY GROWTH IN EPIDIDYMIS

BY

J. R. O'BRIEN, D.M.

Late Graduate Assistant in Pathology, Radcliffe Infirmary, Oxford

Carcinoid tumours, or argentaffinomata, are derived from the Kultschitzky cells, which are normally distributed throughout the mucosa of the gut from stomach to anus. Many hypotheses have been suggested (Masson, 1928), but little is known for certain about the function of these cells, and they are remarkable chiefly by their ability to reduce silver salts. The scarred appendix is the only common site in which these cells may proliferate to form carcinoid tumours, which usually remain small and rarely metastasize.

Similar tumours occur in the small intestine and occasionally in the large intestine and rectum (Cooke, 1931 ; Willis, 1940 ; Stout, 1942), where these slow-growing tumours are usually multiple and are often symptomless until eventually they produce stenosis of the intestine. Secondary deposits from these intestinal growths have been reported in most organs of the body, but the only record of a secondary growth in the testis is by Cope (1930), who found a carcinoid in the testis eight years after resection of a part of the small intestine which contained a single annular primary growth.

Case Report

The patient, aged 73, stated on questioning that when 20 years old he had been hit in the right testis and that the testis had remained hard and slightly enlarged. After a five-years history of indigestion, a laparotomy performed at the Archway Hospital in 1938 revealed an adherent gastric ulcer, for which a posterior gastro-jejunostomy was performed. No other abnormality was noted at this time. In 1944—that is, six years later—he was admitted to the Radcliffe Infirmary under Mr. Olmstead, with an irreducible right inguinal hernia. During the operation for repair of the inguinal canal the right testis was seen to be abnormal and was removed. The patient made an uneventful recovery. The cut surface of the mass removed, which measured 8 by 5 by 2 cm., showed an apparently normal testis, while the epididymis was surrounded by a fibrous mass in which there

were small indefinite, firm, pale-yellow areas. Microscopically, the testis showed normal senile atrophy while the yellow areas showed masses of cells arranged in the classical rosette pattern of an argentaffinoma. The affinity of these cells for silver was confirmed.

The patient was readmitted three months later for further investigations in an attempt to find the site of the primary growth in the hope that it would prove removable. He then considered he was quite well. (Only after the second operation did he realize in retrospect that he had had some constipation and colicky abdominal pain.) Complete *x*-ray examination of the chest and alimentary tract revealed no abnormality; nevertheless, a laparotomy was performed and the terminal 3 ft. (0.9 m.) of small intestine was seen to be studded with about 60 white plaques varying in size from 0.2 to 2 cm. in diameter, distributed at random beneath the serosa. The smaller ones produced little or no puckering of the serosa, while the larger ones caused gross puckering and marked stenosis of the intestine. There was a smooth mass 5 cm. in diameter replacing the lymph nodes in the mesentery, and several small secondary deposits were felt in the liver. Three feet (0.9 m.) of intestine and the mass in the mesentery were removed and a side-to-side anastomosis was performed in order to relieve the partial obstruction.

Photograph of part of the specimen bisected to show three tumours under the muscularis mucosa, one producing stenosis and a portion of the secondary mass in the mesentery

Recovery was uneventful, and two years later, in 1946, the patient had put on weight and felt better than before the operation. Clinical, *x*-ray, and laboratory examinations then showed nothing abnormal. He died in 1947, three and a half years after the original operations, after a short terminal illness. The death certificate states that the cause of death was due to "myocardial degeneration due to secondary carcinoma," with "generalized oedema of the limbs" as a subsidiary cause. No further details are available.

The second specimen is illustrated in the accompanying photograph. There was little muscular hypertrophy at the proximal end of the specimen, yet there was marked stenosis at one point due to a growth some 2 cm. in diameter which had invaded the circular and longitudinal muscle and had produced constriction and hypertrophy of the muscle. The growths varied in size from this largest one to those causing only a slight mound 2 mm. across under the mucosa. On section they were all homogeneous, firm, and whitish yellow in colour. The mass in the mesentery was of similar texture and colour, and appeared to have absorbed much of the mesenteric tissue, causing shortening of the mesentery. Elsewhere the mesentery and glands were normal.

Histological examination of sections taken from many growths of different sizes shows that the neoplastic cells occurred first on the inner aspect of the muscularis mucosa, but that they soon spread through the muscularis while leaving the mucosa intact. The tumours appeared to extend externally to the muscularis, slowly involving the circular muscle, while the mucosa throughout was not involved. The pattern of the neoplastic cells in the primaries and in the mesenteric mass was characteristic, with solid clumps or strands of small polyhedral cells lying in scanty stroma through which ran hypertrophied muscle bundles.

I have to thank Dr. A. H. T. Robb-Smith for permission to publish this case, and for much help in the preparation of the paper.

REFERENCES

Cooke, H. H. (1931). *Arch. Surg., Chicago*, **22**, 568.
Cope, Z. (1930). *Brit. J. Urol.*, **2**, 268.
Masson, P (1928) *Amer. J. Path.*, **4**, 181.
Stout, A. P. (1942). Ibid., **18**, 993.
Willis, R. A. (1940). *Med. J. Aust.*, **11**, 400.

ARGENTAFFIN TUMOUR OF THE ILEUM WITH PERFORATION

BY

IAN S. STEWART, M.D.
Pathologist, Anglo-Iranian Oil Company

AND

G. RUSSELL THOMSON, M.B., F.R.C.S., F.R.F.P.S.
Surgeon, Anglo-Iranian Oil Company

The rarity of epithelial tumours of the small intestine is indicated by the work of Dockerty and Ashburn (1943), who systematically examined the histological details of 130 tumours encountered at the Mayo Clinic in the years 1906–43. Only 30 of these were accepted as argentaffin tumours. Similarly, Raiford (1933) recorded 29 argentaffin tumours of the alimentary tract among 62,000 pathological specimens at the Johns Hopkins Hospital, and, of those, 17 were of the appendix and only 9 in the small intestine. Ariel (1939) succeeded in finding 237 cases in the literature, and Dangremond (1942) added 46 cases to those quoted by Ariel.

The manner in which the tumour comes to light seems to be most commonly as an unexpected finding at necropsy. Of Dangremond's collected cases, 23 were discovered in this way and 15 were found during surgical intervention for acute or subacute obstruction, details of the remaining 8 being either irrelevant or lacking. Again, of Ariel's 11 cases six were discovered post mortem, and all the six reported by Willis (1950) were necropsy findings. Cooke (1931), in reporting 11 cases, describes the case of a man aged 60 who developed severe pain and general abdominal tenderness while under observation for recurrent epigastric pain. At laparotomy a tumour of the ileum 4.5 cm. in diameter was found which had perforated, a quantity of yellow fluid having leaked into the abdominal cavity, and the liver was studded with metastatic nodules. The patient died 14 days after the operation. This case is closely similar to the one now recorded. In reviews of the abundant literature Humphreys (1934) and Ariel (1939) do not mention perforation as a clinical feature of the disorder.

Case History

The patient, a married Iranian woman aged 40, had been well until a year before her admission to hospital. At that time, during the fast of Ramazan, she had fasted for 24 hours and then drank a quantity of iced water. Immediately she was seized by violent abdominal pain, which

lasted several hours. Every two or three weeks after that she experienced the same pain for an hour or so, and on several occasions she vomited during the attack. The pain was always in the right side of the abdomen and the right flank.

Twenty-four hours before her admission to hospital she developed a violent pain over the lower half of the abdomen, accompanied by nausea. Her condition remained unchanged throughout this time. When examined the abdomen below the umbilicus was swollen and tender and no bowel sounds could be heard. No mass could be distinguished on abdominal palpation, but during vaginal examination a hard tender mass was felt above the right fornix.

Operation.—Laparotomy was undertaken through a lower right paramedian incision, and on opening the peritoneum thin pus welled up into the wound. The coils of small intestine were dilated and inflamed as in an ileus, and three tumours were found in the course of the ileum, lying respectively 4, 5, and 12 ft. (1.2, 1.5, and 3.7 m.) from the ileocaecal junction, which was abnormally situated on the left side of the abdomen. The lowest tumour, a mass the size of an orange, had perforated posteriorly, this accident evidently being the cause of the peritonitis. All three tumours were resected and continuity of the gut was restored in each case by a side-to-side anastomosis. No interference with the enlarged mesenteric glands present was attempted. The operation site was dusted with sulphanilamide powder and the wound closed in layers without drainage. An intravenous infusion of glucose-saline was administered throughout the operation and for 12 hours afterwards. A course of 500,000 units of penicillin was given in the post-operative period.

FIG. 1.—Photograph of the three tumours.

The wound healed satisfactorily and the patient left hospital at her own request on the twelfth day. She was the subject of a demonstration at the Abadan Medical Society two months later, and at that time appeared well.

Gross Pathology (Fig. 1).—The uppermost tumour involved about 2 in. (5 cm.) of gut, and appeared simply as a stricture with a diffuse thickening of the wall of the gut on either side of it. The stricture admitted the tip of the little finger, and the gut above it was dilated. The second tumour was also stenosing, but was visible on the peritoneal surface as an irregular collection of yellowish-white plaques. The lowest and largest tumour had a stenosing zone at both its upper and lower ends, between which a sac-like cavity coincided with the irregular yellowish-white mass seen externally. The perforation in the tumour was no more than 1/10 in. (25 mm.) in diameter.

Histology.—Sections of all three masses showed small anaplastic cells, supported by a delicate reticulum of fibrous tissue. The more usual arrangement of well-defined islets embedded in an abundant stroma was nowhere to be found. Sections stained by Levaditi's method showed an abundance of brownish-black granules in the tumour cells (Figs. 2 and 3).

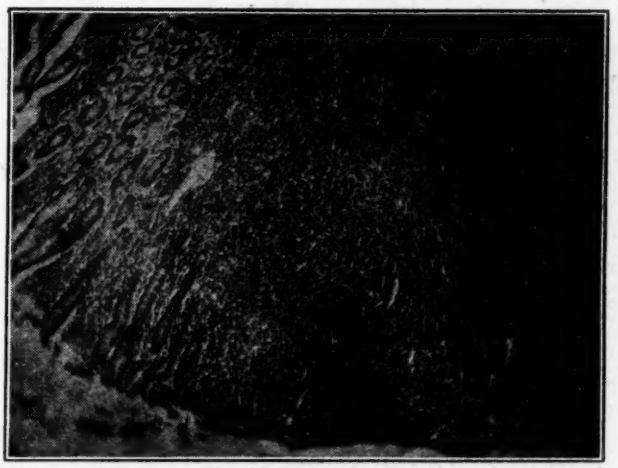


FIG. 2.—Low-power view of intestinal mucosa showing obliteration of normal mucosal epithelium.

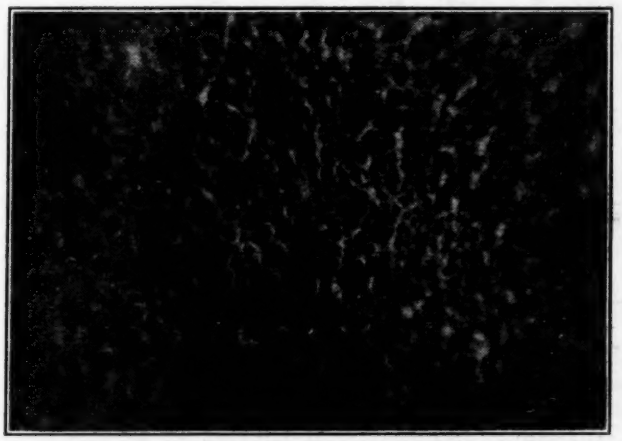


FIG. 3.—High-power view of the tumour cells.

Discussion

Argentaffin tumours of the small intestine are about as frequent as adenocarcinomas (Willis, 1948). They are believed to originate from the Kultschitzky cells of the crypts of Lieberkühn, which have similar staining reactions. Other theories are that they are true carcinomas of the intestinal epithelium, that they are possibly related to basal-cell carcinomas of the skin, that they arise from embryonic rests, and that they originate from the sympathetic nervous system. They are slow in growth, as evidenced by the case reported by Cope (1930), in which many large masses of growth were present and a short-circuit operation was done to relieve almost complete obstruction, the patient returning in eight years in excellent health but with the abdominal masses present and apparently unaltered. This case developed the remarkable feature of a testicular metastasis. Further evidence of the slow progress is provided by the high proportion of the published cases which have been discovered at necropsy, no history of abdominal disturbance being obtained, or very often a history of abdominal pain or altered bowel function insufficient to merit laparotomy.

As a rule the tumours are small, and the one in this case was unusually large, as was that reported by Cooke, which perforated. The histological picture in both was a mass of undifferentiated cells, and not of well-defined cell islets. The larger tumour is possibly more apt to undergo a central necrosis.

Summary

A case of perforation of the small intestine resulting from one of three argentaffin tumours of the ileum is described. Treatment was by excision of all three, restoration of the continuity of the gut, and closure of the abdomen without drainage after liberal application of sulphanilamide powder to the operation sites. The patient recovered uneventfully.

We are indebted to Mr. A. C. Turner, chief medical officer of the Anglo-Iranian Oil Company in Iraq and Iran, for permission to publish this paper, and to Mr. A. F. Hutchisson for the photomicrographs.

REFERENCES

Ariel, I. M. (1939). *Arch. Path.*, **27**, 25.
Cooke, H. H. (1931). *Arch. Surg., Chicago*, **22**, 568.
Cope, Z. (1930). *Brit. J. Urol.*, **2**, 268.
Dangremond, G. (1942). *Amer. J. clin. Path.*, **12**, 223.
Dockerty, M. B., and Ashburn, F. S. (1943). *Arch. Surg., Chicago*, **47**, 221.
Humphreys, E. M. (1934). *Amer. J. Cancer*, **22**, 765.
Raiford, T. S. (1933). Ibid., **18**, 803.
Willis, R. A. (1940). *Med. J. Aust.*, **11**, 400.
—— (1948). *Pathology of Tumours*, p. 414. Butterworth, London.

EFFECTS OF HYPERTHERMIA AND ANTIBACTERIAL AGENTS ON TUBERCLE BACILLI

BY

J. MARKS, M.D., M.R.C.P., Dipl.Bact.
(From the Public Health Laboratory, Cardiff)

Since their first isolation, it has been recognized that the mammalian types of tubercle bacilli will multiply in artificial culture only within a narrow temperature range. The human type is more fastidious than the bovine in this respect, a property which has been correlated with the predilection of the human type for parasitizing those mammals which have relatively low body temperatures. Fever therapy, which has proved useful in general paralysis and in certain gonococcal diseases, has had limited trials in tuberculosis of man and experimental animals. For example, Kling and Rubin (1936) induced pyrexia in tuberculous guinea-pigs by means of periods of short-wave treatment lasting only ten minutes. Duncan and Mariette (1937) treated tuberculous guinea-pigs in a fever cabinet for periods of four to five hours once weekly for 10 weeks. They also treated patients with weekly periods of fever lasting one to three hours. No definite benefit was observed in these trials, but the short or infrequent periods of fever employed could hardly have been expected to have a direct effect on the tubercle bacilli. Some benefit may have been anticipated by the experimenters, however, from the effects of the fever on the defences of the host.

The present work initiates an investigation into the part which hyperthermia may usefully play as an adjuvant to the treatment of tuberculosis with streptomycin and chemotherapy, whose present limitations are becoming increasingly evident. The chief defects of streptomycin treatment are the restrictions imposed on dosage by toxicity, the frequent appearance of resistant strains during its course, and the failure of response of those lesions into which penetration of the antibiotic is difficult. In such lesions it seems that the appearance of resistant mutants is facilitated owing to the exposure of the bacilli to sublethal concentrations of streptomycin. The experiments described below show that the sensitivity of tubercle bacilli to streptomycin may be considerably enhanced by cultivating the organisms at a temperature above the optimum. The temperature chosen was 40° C. (104° F.), which is one readily attained in fever therapy. The strains examined were all of the human type (judged by cultural characteristics). *Para*-aminosalicylic acid and a thiosemicarbazone (*p*-acetylaminobenzaldehyde thiosemicarbazone), which are the most promising of the newer synthetic drugs, were also investigated, while mercuric chloride provided the contrast of a simple disinfectant..

Experimental Methods

Sensitivity titrations at 40° C. (±0.2° C.) were incubated in a large insulated water-bath (55 by 40 cm.) fitted with a "sunvic" unit. Owing to the temperature gradient between the centre and walls of the bath, the tubes of medium were not all at the same temperature, but by lagging the walls and avoiding the periphery of the bath the range was limited to 39.8°–40° C. A bath of the same type with a temperature range of 36.8°–37° C. was used for control titrations. Similar results were obtained, however, when controls were incubated in a 37° C. air incubator in which the temperature of the medium reached 36.5°–37° C.

The culture medium employed, derived from Dubos's work, had the following composition : KH_2PO_4 1 g., Na_2HPO_4 3.1 g., sodium citrate 1.5 g., $MgSO_4$ 0.6 g., asparagin 2 g., "tween" 80 0.5 ml., glass-distilled water 1 litre. It was dispensed in 2.5-ml. amounts in ¼-oz. (7-ml.) bijou screw-capped bottles and autoclaved at 10 lb. (0.7 kg. per cm.²) pressure for 15 minutes. Before inoculation, 0.1 ml. of a 9% solution of bovine albumin was added aseptically to each bottle. The thiosemicarbazone was autoclaved, but the *p*-aminosalicylic acid (sodium salt) and mercuric chloride were sterilized by heating 1% and 0.1% solutions, respectively, in a boiling water-bath for 15 minutes.

The strains of tubercle bacilli investigated had been recently isolated from cases of pulmonary tuberculosis. Before use they had undergone three weekly subcultures in Dubos's medium after their primary isolation on solid medium. The grown cultures were sometimes stored at 4° C. for short periods until required. One drop (approximately 0.03 ml.) of such a culture was used to inoculate each tube of a titration. The strains whose streptomycin sensitivity was studied were chosen from a group somewhat more resistant than the average, being inhibited (at 37° C.) by concentrations ranging from 0.25 to 4 units per ml.

Readings were made by comparing the turbidity of cultures with barium sulphate standards in bijou bottles. The amount of growth was recorded by a numeral representing the amount of barium chloride in mg. per 100 ml. giving a similar opacity in the presence of an excess of 1% sulphuric acid. Opacities less than 0.6 were recorded as "trace" and above 40 were not distinguished from 40. The intervals between standard tubes were 100%, but intermediate values were estimated when possible.

Results

Not all of the strains of tubercle bacilli tested gave sufficient growth at 40° C. to permit satisfactory titrations. Of 40 strains examined on this point, 10 developed opacities of less than 2.5 after seven days' incubation

at 40° C. Most experiments were performed on strains growing fairly well at 40° C., but those on strains growing less well gave similar results. Stocks stored for some weeks at 4° C. grew less readily at 40° C.

The first part of the accompanying Table records the streptomycin sensitivity of one strain, determined at 37° C. and at 40° C. The titration at 40° C. was transferred, after the period stated, to 37° C. to find out whether the effect of hyperthermia was permanent. In this example the sensitivity to streptomycin was increased 16 times by cultivation at 40° C., and the increase largely persisted after transfer to 37° C. Twelve other strains that were tested against streptomycin increased in sensitivity between 8 and 32 times at 40° C., the effect being somewhat greater with the strains growing poorly at this temperature.

Sensitivity to Antibacterial Substances of Tubercle Bacilli (Human Type) Grown at (a) 37° C. and (b) 40° C. with Subsequent Transfer to 37° C.

Antibacterial Substance	Titration	Temperature of Incubation	Period of Incubation	*Degree of Growth with Given Concentration of: (i) Streptomycin in Units per ml.								
				4	2	1	0·5	0·25	0·12	0·06	0·03	Nil
Streptomycin ..	(a)	37° C.	7 days	0	0	0	1·2	10	15	15	15	15
	(b)	40° C.	7 ,,	0	0	0	0	0	0	0	1·2	10
	(a)	37° C.	Further 7 days	0	0	1·2	10	15	20	30	30	30
	(b)	37° C.	7 days after transfer	0	0	0	0	0	5	15	20	20
				(ii) Thiosemicarbazone in mg./100 ml.								
				1	0·5	0·25	0·125	0·062	0·031	0·016	0.008	Nil
Thiosemicarbazone ..	(a)	37° C.	7 days	0	0	0	0·6	1·2	0·6	10	1·2	20
	(b)	40° C.	7 ,,	0	0	0	0	0	0	Trace	0	10
	(a)	37° C.	Further 7 days	0·6	Trace	0·6	5	10	0·6	20	10	40
	(b)	40° C.	,, 7 ,,	0	0	Trace	0·6	Trace	0·6	0·6	Trace	20
	(a)	37° C.	,, 7 ,,	1·2	2·5	5	10	15	10	20	15	40
	(b)	37° C.	7 days after transfer	0	0	0·6	2·5	Trace	2·5	1·2	0·6	30
				(iii) Mercuric chloride in mg./100 ml.								
				6·4	3·2	1·6	0·8	0·4	0·2	0·1	0·05	Nil
Mercuric chloride ..	(a)	37° C.	7 days	0	0	0	5	10	10	10	10	10
	(b)	40° C.	7 ,,	0	0	0	Trace	0·6	1·2	2·5	5	5
	(a)	37° C.	Further 7 days	0	0	0	20	30	30	30	30	30
	(b)	37° C.	7 days after transfer	0	0	0	5	10	10	10	20	20

* Recorded in terms of barium sulphate standards (see text). Traces of growth (<0·6) denoted by "trace."

The effect of hyperthermia on the sensitivity of tubercle bacilli to *p*-aminosalicylic acid was the same as on streptomycin sensitivity, so does not need to be recorded separately. Concentrations from 2 mg. to 0.002 mg. per 100 ml. were chosen according to a preliminary estimate of sensitivity. Strains of high resistance, derived from patients who had undergone treatment with the drug, increased in sensitivity at 40° C.

In titrations of sensitivity to thiosemicarbazone there was often difficulty in determining the end-point. This was due to the common finding of small amounts of growth in several successive twofold dilutions of drug and also to what appeared to be the frequent occurrence of variant bacilli of high resistance. However, those titrations with definite end-points did show an increase in sensitivity at 40° C. as with streptomycin and *p*-aminosalicylic acid. A typical set of titrations of sensitivity to thiosemicarbazone is recorded in the second part of the Table. Incubation at 40° C. was continued for 14 days before transferring to 37° C., but both 7- and 14-day readings are given.

When growth was sufficient for a satisfactory titration, hyperthermia had little effect on sensitivity to mercuric chloride. Although the end-points of titrations at 40° C. showed little or no alteration from those at 37° C., growth was impaired to varying degrees. Representative titrations are given in the last part of the Table.

Discussion

On two occasions during the examination of a few strains growing poorly at 40° C. heavy growth was observed in a single tube of a sensitivity titration (not the control tube). This finding suggests that growth which appears at 40° C. results from the activity of only a fraction of the inoculum. This explanation is supported by the failure of some stock strains of tubercle bacilli to give consistently successful subcultures at 40° C. Further work is required to clarify the mechanism responsible for the experimental findings, but as a working hypothesis it appears reasonable to suppose that the great increase of sensitivity to streptomycin and *p*-aminosalicylic acid obtained by cultivating at 40° C. is due to the requirement for growth of the presence of variants insensitive both to the drug and to the higher temperature. Such variants would be much rarer than bacilli resistant to the drug alone.

The sensitivity to streptomycin or *p*-aminosalicylic acid of a strain examined by the technique described above is only an expression of the incidence in the inoculum of resistant variants whose degree of resistance is in inverse ratio to their frequency. The reduction in the number of viable resistants due to cultivation at 40° C. is therefore reflected in the increase in sensitivity. With thiosemicarbazone, the degree of resistance and the infrequency of incidence of resistant variants do not appear to be correlated in this way. Consequently the effect of cultivation at 40° C. may sometimes be partly obscured by the irregular appearance of variants with high resistance to the drug. Similar reasoning suggests that the small increase in sensitivity to mercuric chloride observed in titrations at 40° C. is due to all the bacilli of a strain having approximately the same susceptibility to the disinfectant. This homogeneous reaction is also shown by different strains, all of those tested at 37° C. being inhibited by the same concentration of mercuric chloride.

If the conditions of these experiments at 40° C. could be paralleled *in vivo* the effectiveness of treatment with the therapeutic agents examined might be expected to show a considerable improvement. It is not safe to

maintain a temperature of 40° C. (104° F.) in patients for long periods, but since it is customary to administer streptomycin by a single dose daily it might be practicable to enhance the effect of the streptomycin by inducing fever during the period of maximal concentration in the tissues. Unfortunately, the effects on tubercle bacilli of short exposures to hyperthermia and streptomycin cannot be conveniently studied *in vitro* owing to the difficulty of reproducing the changing streptomycin concentrations that occur in a treated patient.

Smith and Vollum (1950) observed that certain cases of tuberculous meningitis benefited by the administration of tuberculin intrathecally during treatment with streptomycin. Their records show that a febrile reaction was provoked by the tuberculin injections, and it is possible that the beneficial effect of these injections was due, in whole or part, to the combination of the fever they produced and streptomycin. As injections of tuberculin are hazardous, it is important to ascertain whether they can be replaced by fever therapy, which may be applied in a controllable form

It is hoped that animal experiments will provide further evidence of the synergism of hyperthermia and streptomycin and *p*-aminosalicylic acid. Such experiments should not, however, preclude clinical trial, because the reaction of man to infection by the tubercle bacillus cannot be exactly reproduced in any animal. As a direct action on the organism is aimed at, the induction of a temperature of at least 104° F. (40° C.) should be attempted ; it should be reached approximately one hour after the injection of streptomycin and be maintained for four to six hours. The number of such courses would vary with the tolerance of the patient, but it is probable that they would best be given on successive days. *Para*-aminosalicylic acid could be administered at the same time.

Summary

About 25% of strains of *Myco. tuberculosis* (human type) grew very poorly in Dubos's medium at 40° C. The growth of the remainder was slightly or moderately impaired.

The sensitivity of strains growing sufficiently well for testing at 40° C. was considerably increased to streptomycin, *p*-aminosalicylic acid, and often to thiosemicarbazone, but not to mercuric chloride.

Reasons are advanced for trying a combination of hyperthermia with streptomycin and *p*-aminosalicylic acid treatment in tuberculosis of man caused by the human type of bacillus.

I am indebted to Dr. B. A. D. Stocker for a discussion of the mechanism of the phenomena recorded, and to Dr. G. S. Wilson and Dr. Scott Thomson for improvements in the presentation.

REFERENCES

Duncan, G. R., and Mariette, E. S. (1937). *Amer. Rev. Tuberc.*, **36**, 387.
Kling, D. H., and Rubin, H. M. (1936). Ibid., **34**, 498.
Smith, Honor V., and Vollum, R. L. (1950). *Lancet*, **2**, 275.

The whole undergraduate population of the Queen's University, Belfast, was examined radiologically once in the academic year 1950–1, states the third annual report of the student health medical officer. Seventeen cases of active tuberculosis were noted among the 2,368 students, and eight of these cases had been in normal health a year previously. No reason for their breakdown in health could be found in their mode or conditions of life, and the source of their infection remained unknown.

AN UNUSUAL METHOD OF TREATING HYDROCEPHALY

BY

AGNES U. CAMPBELL, M.B., Ch.B., M.R.C.O.G.
Senior Registrar in Obstetrics and Gynaecology, City General Hospital, Stoke-on-Trent

Nowadays the treatment of hydrocephalus is more or less standardized : the head is collapsed per vaginam either by puncturing it with a sharp instrument, with or without drainage through a cannula, or by the passage of a hollow instrument up the spinal canal into the brain.

The following case is presented because the above methods failed when attempted per vaginam. The method employed was puncture of the head and drainage through a cannula, but it was carried out through the maternal abdominal wall. This method is not claimed as original. It is mentioned on several occasions in the literature, but no details are given. It is this absence of detail that has prompted me to publish the following case.

Clinical History

A primigravida, aged 31 and married eight years, first attended the antenatal clinic on September 20, 1949. She was then 22 weeks pregnant. The uterus corresponded in size with the duration of amenorrhoea. No abnormality was detected. Her blood pressure was 110/60 ; her urine was clear.

On November 17, when she was 30 weeks pregnant, the uterus was the size of a 34-weeks pregnancy. The presenting part was thought to be a breech, but the head could not be identified in the fundus. A radiograph showed a single foetus, of about seven months' maturity, presenting as a breech. The head was extended and appeared slightly enlarged. On November 19 external cephalic version was attempted, but was unsuccessful. It was then decided that an abnormal foetus with hydrocephaly was likely, and that a further *x*-ray examination should be made in three weeks, by which time there should be no doubt about the diagnosis.

At 9 a.m on December 8, when 33 weeks pregnant, the patient was admitted to hospital in early labour. The membranes had just ruptured and there had been a sudden gush of liquor amnii. The findings on abdominal palpation were difficult to interpret, but a large soft swelling could be felt in the fundus, and this was thought to be a hydrocephalic head. The foetal heart rate was 120 per minute. On rectal examination the presenting part was thought to be a breech, in mid-cavity, with the os dilated to one to two fingerbreadths. A radiograph was requested, but the *x*-ray plant was under repair and could not be used. Uterine contractions were quite strong and were occurring every seven minutes.

At 1 p.m., on vaginal examination, a complete breech was felt, which had descended as far as the ischial spines, and the os was dilated to four fingerbreadths. By 4 p.m. the contractions were much weaker and no advance had been made. In an effort to stimulate contractions a course of stilboestrol was given—10 mg. quarter-hourly for 12 doses. The pains became stronger again about 10 p.m., but after two hours of these stronger pains there was still no progress.

At 12 midnight an examination under general anaesthesia —gas, oxygen, and ether—was carried out. The large soft swelling in the fundus was now definitely identified as a hydrocephalic head. No further dilatation of the cervix had taken place. Since the progress of labour had been arrested, the anterior leg was brought down so that the half-breech could act as a cervical dilator. At 1 a.m. she

was fully dilated and began bearing down strongly. By 2 a.m. both legs were delivered as far as the knees. At this stage further progress ceased in spite of strong bearing-down efforts.

At 2.15 a.m. a general anaesthetic—gas, oxygen, and ether—was again administered to enable a breech extraction and puncture of the aftercoming head to be carried out. In spite of strong traction on the legs it was impossible to deliver the baby further than the thighs. It was realized that the hydrocephalic mass plus probably some other abnormality was causing obstruction at the pelvic brim. Foetal ascites and extended arms were excluded as possible other causes of obstruction by palpating the foetal abdomen and feeling the arms lying along the trunk. Intra-uterine exploration failed to reveal the tumour of the neck. (The tumour must have been mistaken for the face.)

The following more usual methods of collapsing the hydrocephalus were now considered or attempted in turn, but these failed or were impracticable:

1. The absence of a spina bifida ruled out the passage of a gum-elastic catheter along the spinal canal.

2. Spondylectomy, another method of entering the spinal canal, was not attempted, because the foetal spine was not visible.

3. The longest trocar and cannula, 6 in. (15 cm.) in length, was now passed along the foetal back as far as the postero-lateral sinus of the skull, but its progress then became arrested by the large flange on its end overlapping the under surface of the maternal pubic bone. The Drew-Smythe catheter was substituted, but the soft metal bent when pressure was exerted. A fine lumbar puncture trocar and cannula was successfully introduced into the uterus past the maternal pubic bone and the skull was punctured. Only a little cerebrospinal fluid escaped and then the cannula blocked. A syringe was attached to the cannula high up in the uterus in an effort to unblock it, but access was so difficult that the syringe could not be operated.

4. Internal cephalic version might have been successful earlier, but the uterus was now too firmly retracted round the foetus.

It was therefore decided that an attempt to puncture the head through the maternal abdominal wall should be made. The bladder was again emptied by catheter and several ounces of urine were withdrawn.

A point 1½ in. (3.75 cm.) below and to the left of the umbilicus was selected as the site of puncture. The left side was chosen because the occiput was on the left, the face on the right. A lumbar puncture needle was now easily pushed through the maternal abdominal wall, uterus, and hydrocephalic skull. Blood-stained C.S.F. escaped through the cannula. It became blocked on several occasions with brain matter, but the blockage was dislodged by forcing saline from a syringe through the cannula. The rate of drainage of C.S.F. was accelerated by bimanual compression of the foetal skull. Throughout the manœuvre the mother remained in the lithotomy position and the foetal legs were left hanging over the edge of the bed. When the head had collapsed sufficiently to cease to be an obstructing factor, the foetus more or less fell out of the maternal pelvis, and the cannula had to be very rapidly withdrawn.

The third stage of labour was completed normally. The puerperium was uneventful.

The foetus was stillborn, female, and weighed 5½ lb. (2.5 kg.). The head was still obviously hydrocephalic (see illustration). A large tumour was present on the front of the neck. The cervical spine seemed to be missing and the head was hyperextended.

Post-mortem examination confirmed the above findings. In addition, it was found that the cervical vertebrae were fused as in the Klippel–Feil syndrome. No other congenital abnormalities were found. Section of the cervical tumour showed only a mass of myxomatous tissue.

Discussion

The above method of treatment is obviously not the one of choice in the less-complicated cases of hydrocephaly, for there is considerable risk of injuring the maternal bladder and bowel. The risk of injuring the bladder is lessened by emptying it with a catheter first and by puncturing the abdominal wall at the level of the umbilicus. The bowel is less likely to be injured at the above site of puncture except in cases which have had a laparotomy and may have adhesions to the anterior abdominal wall.

A longer trocar and cannula would, of course, have made puncture of the head from below possible.

As mentioned above, another abnormality was suspected, because it is usually possible to deliver a hydrocephalus with breech presenting, at least as far as the umbilicus. The other obstructing features here were the tumour of the neck and the Klippel–Feil deformity of the cervical spine.

Instead of using this method only when others fail, a wider application could be claimed for it. Most obstetricians agree that it is desirable to induce labour once hydrocephaly has been diagnosed. Induction of labour when the hydrocephalic foetus is presenting as a breech is difficult because artificial rupture of the membranes is unreliable. In addition external cephalic version is often unsuccessful in these cases because of the difficulty of moving the large head. It is never wise to be too persistent in attempting version in these cases, because of the very real danger of rupturing the uterus. In such cases puncture of the head as above should facilitate version.

When the hydrocephalic head presents, induction of labour by puncture of the head from below is simple, even when the cervix has to be dilated first. Rupture of the membranes *per se* is again an unreliable method of induction, for the head does not closely fit the cervix. It would be hard in such cases to justify any more risky procedure, for the puncture through the maternal abdominal wall would have to be nearer the bladder when the hydrocephalic head is the presenting part.

Summary

A case of hydrocephalus complicated by a tumour of the neck and deformity of the cervical spine is described. Delivery was made possible by puncture of the head through the maternal abdominal wall.

This method of treatment and the more usual methods are contrasted.

No references are quoted, because this method is only mentioned *en passant* in the literature studied.

I wish to thank Mr. Harold Burton, obstetrician and gynaecologist at this hospital, for permission to publish this case and for helpful criticism in preparing this article. I am also indebted to Dr. Leo Sefton for performing the post-mortem examination and taking the photograph from which the sketch was made.

Medical Memoranda

A Case of Acute Gastric Haemorrhage

The following case illustrates the difficulty which may be encountered in deciding on the source when performing an emergency operation for gastro-duodenal haemorrhage.

Case Report

A short fat schoolmaster aged 51 was admitted to the medical wards of the West Suffolk General Hospital on the afternoon of February 4, 1950. On the previous night, at 11 p.m., he had been violently sick. The vomit contained food and beer, but no blood. He then felt faint and lay down for an hour, after which he was carried to bed, and slept well. He felt well the next morning. During the course of the morning he had three large melaena stools and again felt faint.

On admission to hospital he was feeling dizzy, but had no pain. He gave a history of occasional attacks of indigestion, always settled by milk of magnesia. There was no loss of weight; his bowels opened regularly, and occasional bright red blood came from bleeding piles. His general condition was good; his blood pressure was 150/90, and pulse 92. The next morning he had another large melaena stool, his blood pressure dropped to 100/70, and his haemoglobin was found to be 6.62 g.%.

I was asked to see him that evening with a view to surgery. He was thought to have a bleeding duodenal ulcer. I agreed with this diagnosis, and thought that at his age, and because he had had a second haemorrhage after admission to hospital, surgery was indicated. Sigmoidoscopy to 20 cm. showed the bowel full of melaena stools, and proctoscopy revealed small first-degree haemorrhoids. During the night he was given 3 pints (1.7 litres) of blood slowly, and the next morning his blood pressure was 120/70.

Operation was carried out that evening under anterior abdominal field block with 1/2,000 amethocaine hydrochloride and cyclopropane and oxygen. At operation his stomach, duodenum, and upper part of the ileum contained no blood. There was no duodenal ulcer, and no gastric ulcer could be felt on the anterior wall of the stomach or on the posterior wall after opening the lesser sac. The liver appeared normal. The caecum was next examined and found to be full of blood. The ileum was followed up and was found to be full of blood until about the junction with the jejunum, where a tumour about the size of a small tangerine was found. There was no blood in the jejunum above this. The tumour was fixed in the antimesenteric border of the jejunum and had prominent arteries and veins coursing over it. It was presumed to be an adenoma and the cause of the haemorrhage. It was resected with 2 in. (5 cm.) of normal bowel on either side and end-to-end anastomosis performed.

The patient made an uninterrupted recovery and was discharged from hospital on February 18 with a haemoglobin of 10.76 g.%.

On examining the tumour after removal it was obviously not an adenoma, and no ulceration could be seen. Section showed it to be a leiomyoma, and confirmed that there was no ulceration; however, the possibility of another source of haemorrhage was not considered.

On February 23 the patient had another copious melaena stool, and this was repeated on the 24th. I saw him on the 25th and, much against his will, persuaded him to come into hospital. On admission to the surgical ward on the 25th his haemoglobin was 6.62 g.%. He had no pain, but felt slightly dizzy.

Conservative treatment was adopted and he had no further melaena stools. After 14 days, barium meal and follow-through was performed; this was normal. Barium enema also showed no abnormalities. A fractional test meal was within normal limits.

The patient had been unwilling to have a gastroscopy, but he was at last persuaded, and this was performed on March 20. Visualization was normal; the pylorus was seen, low folds, and a thin mucosa. There was a small scar with low folds radiating from it just above the angulus on the lesser curve.

He was discharged on April 3 with a haemoglobin of 11.5 g.% and advised to keep on a gastric ulcer diet. His piles were injected.

When last seen on October 20 he was very well and had had no indigestion, except when he took meals at the school canteen.

Comment

Numerous examples have been published of leiomyomas having caused fatal intestinal haemorrhage, but on section these have all shown ulceration of the mucosa covering them, and it is impossible to imagine gross haemorrhage occurring without definite ulceration.

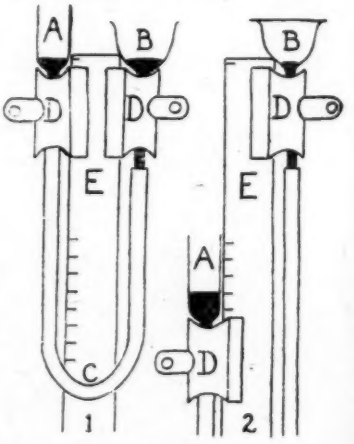
At operation the stomach had been very carefully examined, because it was realized that there may be no blood in the stomach, duodenum, or jejunum when an ulcer has stopped bleeding for some hours before an operation, but I have no doubt that the scar seen on gastroscopy was that of a healed ulcer which had been responsible for the haemorrhage on both occasions.

At a discussion on gastro-duodenal haemorrhage, held at the Royal Society of Medicine on December 7, 1949, Mr. A. M. Desmond advocated immediate gastroscopy prior to operation, and this is a case in which it might have been of great assistance.

T. M. WILLIAMS, F.R.C.S.,
Consultant General Surgeon, West Suffolk General Hospital.

Capillary Resistance Test: A Simple Negative-pressure Method

At the Brighton General Hospital the following device for carrying out capillary resistance has proved useful. It is simpler than those I have found described in the literature available. The principle is that of Boyle's law apparatus used in elementary physics laboratories. The method is indicated diagrammatically. A is a small funnel and B a thistle funnel, with wide stems. These are connected by wide tubing, C, and fixed by large spring paper-clips, D, to an ordinary school ruler, E, marked in centimetres. Their stems pass through the springs of the clips, which support and keep them in place.



Mercury is poured into A or B until the level is roughly as shown in the diagram (1). B is then applied to the skin to be tested, greased if necessary, and A is lowered as in the diagram (2), producing a negative pressure in B measured by the difference between the mercury levels, which is read direct from the ruler.

W. A. BOURNE, M.D., F.R.C.P.

Reviews

A DOCTOR'S LIFE

Leaves from a Doctor's Life. By Sir Philip Panton. (Pp. 232; illustrated. 18s.) London: William Heinemann. 1951.

Philip Panton was born on December 26, 1877, in the little Dorset town of Wareham, the son of a brewer of yeoman stock. He inherited his artistic bent—for pathologists can also be artists in their work—from his mother, the daughter of W. P. Frith, R.A., whose pictures "Derby Day," "The Railway Station," and "Ramsgate Sands" drew crowds to the Royal Academy when they were first exhibited. Incidentally, Panton records a remarkable ghost story which he heard from his grandfather. Philip Calderon, R.A., was the author's godfather.

After leaving preparatory school Panton went to Harrow, then under the able sway of Dr. Welldon. He met there L. S. Amery, whom Welldon considered his best pupil, Winston Churchill, "that strangest of schoolboys and most brilliant of war Prime Ministers," and G. M. Trevelyan, "most readable of historians." From Harrow Panton proceeded in due course to Trinity College, Cambridge, where Walter Fletcher was his director of studies. He admits he was not a strenuous student, finding time for cricket, tennis, or football in the afternoons, but after taking his natural sciences tripos he went to St. Thomas's Hospital, where life was more earnest.

Qualified M.B.Cantab., Panton took house appointments at his hospital, went as ship-surgeon for a voyage round the world, and, after a period in the laboratories of St. Thomas's Medical School, became clinical pathologist at the London Hospital. Here he worked steadily for thirty years, training generations of students in pathology and winning the friendship and esteem of his colleagues on the hospital staff. His reputation in pathology was well known to "London" men, but it was less fully appreciated by the outside world. This was because of Panton's retiring personality, for he never published much and kept his wisdom for his students. When the second world war came, Panton was called to the Ministry of Health as consultant adviser in pathology. As he relates in this book, it was difficult for so strong an individualist to adapt himself to working with Civil Servants, whose outlook in many matters seemed to be obstructive and hampering. But the experiment succeeded. On better acquaintance, mutual respect ensued, harmony prevailed, and Panton efficiently organized the hospital laboratory services on a large scale. In this task he never spared himself, and he crowned his career by putting the finishing touches to the work, which is of enduring value for the diagnosis and treatment of disease, before he retired. His outstanding services were recognized by the bestowal of a knighthood.

In these pages Panton has crystallized the experiences and reflections of a lifetime. Readers, especially those of riper years, will enjoy his frank and independent views on voluntary and State hospitals, doctors and medical students, pathology, the Ministry of Health, and the art of growing old. Panton was always a delightful companion, and, like Heraclitus, "his pleasant voices, his nightingales," are still awake in this book which he has given us.

ARTHUR S. MACNALTY.

TEXTBOOK OF HEART DISEASE

Heart Disease. Its Diagnosis and Treatment. By Emanuel Goldberger, B.S., M.D. (Pp. 652; 90 illustrations. £3 10s.) London: Henry Kimpton. 1951.

The general plan and scope of this book are commendable. It is divided into five sections. In the first the author discusses the normal heart as shown by physical examination, recording methods, radiology, electrocardiography, and special tests. In the second he considers the abnormal heart in similar manner. The third section is on heart failure, shock, syncope, angina pectoris, neurocirculatory asthenia, and cardiac arrhythmias. In section four he classifies the various forms of heart disease according to aetiology, and describes them individually. Finally, in the fifth section he discusses heart disease in relation to pregnancy, general surgery, anaesthesia, and employment.

Little has been neglected in this survey, and on the whole the factual and explanatory details are accurate and orthodox; yet the work is not entirely satisfactory. There are 90 illustrations, but they are mostly diagrams, and they are not listed in the table of contents. There are plenty of references at the end of each chapter, but none are referred to in the text. The style, though crisp enough in many places, is clumsy, almost careless, in others. For example, the introduction to the section on cor pulmonale is as follows: "Although the clinical picture of progressive right-sided heart failure resulting from chronic cor pulmonale is similar, regardless of the etiology of the cor pulmonale, the more common conditions responsible for chronic cor pulmonale will be separately described below." A textbook is unlikely to be rated very highly if the author is indifferent to natural figures, references, and good English (or American).

Moreover, Dr. Goldberger does not seem sufficiently familiar with some aspects of his subject. What he writes on radiology is consistently weak, and the chapters on congenital heart disease, rheumatic fever, and cor pulmonale, conditions of great current interest, are poor, particularly from the clinical point of view. Several statements in these three chapters seem incompatible with much real experience of the matter described.

Nevertheless, despite these rather serious defects, Dr. Goldberger's book ranks as one of the better treatises on heart disease written since the second world war. It is up to date, and its permanent strength lies in its simplicity, completeness, and balance.

PAUL WOOD.

SPIRITUAL HEALING

Psychology, Religion, and Healing. By Leslie D. Weatherhead, M.A., Ph.D., Hon.D.D.(Edin.). (Pp. 544. £1 5s.) London: Hodder and Stoughton. 1951.

It is only in comparatively recent times and in selected communities that psychiatry has attempted to take over the healing of the mind from the preachers. It has yet to be shown by comparative results that this always constitutes an advance. This is especially the case with psychotherapy in the neuroses. For instance, the failure of Freudian and other doctrinaire methods to cope with the problem of the alcoholic has allowed religiously orientated systems like Alcoholics Anonymous to come to the fore again and show they have something more practical and successful to offer.

In his writing and work on spiritual healing, however, Dr. Weatherhead has for many years tried to bridge the present gulf and synthesize religious and modern psycho-

therapeutic approaches. In his latest book he examines and compares the various methods of religious and psychological healing used throughout the ages. He includes a study of biblical miracles, exorcism of demons, Christian Science, and the like, and discusses at length the theories of Freud, Jung, and Adler. Emphasis is laid on current psychosomatic theories of the causation of bodily illness to explain some of the successes obtained in religious healing.

Psychiatry might gain much from a more searching examination of why spiritual healing is often more successful than its own practices in helping some people in states of mental conflict. A greater certainty of approach, maturer handling of group techniques, and more positive guidance all play a part. Greater realism may be shown in the mobilizing of repressed emotions.

But the dangers inherent in lay or pastoral psychotherapy are obvious, especially in the severer forms of mental disorder. Dr. Weatherhead stresses the absolute need for the closest co-operation between doctors and pastoral psychotherapists attempting such work. He tries to be fair to all approaches, pointing out that leucotomy and E.C.T. may be needed in selected patients, and spiritual guidance or a probing of the unconscious in others. He shows tolerance and understanding towards the many different methods necessary to help the regaining of spiritual balance by "all sorts and conditions of man."

WILLIAM SARGANT.

MAN'S ORIGIN

Wonderfully Made. Some Modern Discoveries about the Structure and Functions of the Human Body. By A. Rendle Short, M.D., F.R.C.S. The Second Thoughts Library, No. 6. (Pp. 160. 6s.) London: The Paternoster Press. 1951.

This little book has for its main object the consideration of the eternal and insoluble question of man's origin. The author, a well-known surgeon who has a special knowledge of physiology, in the first place describes briefly several of the chief physiological mechanisms of the body. He does this in clear and simple language, and with the use of many apt but homely analogies, so that the ordinary layman cannot fail to understand the meaning and to appreciate why the title of the book was chosen.

In the last section he compares three of the main views held concerning man's origin—entelechy, Darwinism, and divine creation. The author rejects the first, accepts the second with certain definite limitations, and gives logical reasons for accepting the third. He points out some difficulties which arise if natural selection is regarded as the only process leading to evolution, and quotes several distinguished modern scientists in support of his view.

When once a scientific theory is accepted as a working basis there is always the danger that it may be regarded as a proved fact, and critics of the theory may not be treated altogether fairly. For many years any doubt cast on the atomic theory, even by recognized and distinguished physicists, was frowned upon. Theologians are not the only persons who dogmatize. For many years the theory of evolution by natural selection has held the field, but from a perusal of this book it is clear that it may not prove to be the complete answer to the question of man's origin.

V. ZACHARY COPE.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Community Mental Health in Practice. Proceedings of a Conference on Mental Health held at St. Pancras Town Hall, London, N.W.1, March 12–13, 1951. (Pp. 67. 3s. 6d.) London: National Association for Mental Health. 1951.

The Testing of Hearing Aids. By D. B. Fry and P. Denes. Booklet No. 490. (Pp 39. 1s.) London: National Institute for the Deaf. 1951.

Christianity and Human Relations in Industry. By Sir George Schuster, K.C.S.I., K.C.M.G., C.B.E., *M.C.* (Pp. 128. 6s. 6d.) London: The Epworth Press. 1951

Milk Testing. By J. G. Davis, D.Sc., Ph.D., F.R.I.C. (Pp. 260. 15s.) London: Dairy Industries. 1951.

Understanding Your Child. By L. Stebbing. (Pp. 107. 5s. 6d.) London: New Knowledge Books. 1951.

The Snail Hosts of Bilharzia in Africa. By A. Mozley, D.Sc., Ph.D., F.R.S.Ed. (Pp. 78. 9s.) London: H. K. Lewis. 1951.

The Story of St. Luke's Hospital. By C. N. French, C.M.G., C.B.E. (Pp. 212. 8s. 6d.) London: William Heinemann. 1951.

Diet Book of the David Lewis Northern Hospital, Liverpool, 1951. (Pp. 68. 7s. 6d.) Liverpool: Lee and Nightingale. 1951.

Exercises After Childbirth. By G. Behn, M.C.S.P. (Pp. 32. 3s.) Edinburgh: E. and S. Livingstone. 1951.

Orthopaedic Nursing. By M. Powell, S.R.N., M.C.S.P. (Pp. 400. 25s.) Edinburgh: E. and S. Livingstone. 1951.

Cayetano Heredia. By Dr. C. E. Paz Soldan. (Pp. 289. No price.) Lima: Publicaciones del Instituto de Medicina Social. 1951.

De la Méthode en Médecine. By Professor R. Crachet. 2nd ed. (Pp. 248. No price.) Paris: Presses Universitaires de France. 1951.

Rapports, Communications, Discussions. Séances d'Inauguration de la Société Française de Dermatologie et de Syphiligraphie Filiale Marseillaise. (Pp. 470. No price.) Marseilles: Editions M. Leconte. 1951.

Lehrbuch der Röntgendiagnostik. By H. R. Schinz and others. Part 4, 5th ed. (Pp. 513. M. 84.) Stuttgart: Georg Thieme. 1951.

Angewandte und Topographische Anatomie. By Professor G. Töndury. (Pp. 416. M. 70.) Stuttgart: Georg Thieme. 1951.

In selecting material for *The Medical Annual, 1951* (John Wright and Sons, Ltd., 27s. 6d.), the editors, Sir Henry Tidy and Mr. A. Rendle Short, have again been remarkably successful, for the many distinguished contributors have reviewed not only the latest progress in medical science but have included useful notes on some of the common and troublesome conditions often seen in general practice. Dr. Avery Jones, for instance, writes about aerophagy and flatulence, and Mr. F. W. Watkyn-Thomas discusses the indications for the use of hearing-aids and the management of deaf patients generally. Professor Lambert Rogers sounds a warning about the seriousness of what is called in the U.S.A. "wringer injury": the patient is usually a child who has had its fingers, or even its whole arm, drawn into the electrically operated wringer of a modern washing-machine. Among descriptions of more obscure conditions, that of Q fever is particularly worth reading. As in past years, the volume is copiously illustrated, and there are the usual lists of pharmaceutical preparations and books of the year. In spite of the greatly increased costs of production the price of this year's *Medical Annual* is only half a crown more than last year's volume.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY DECEMBER 1 1951

THE ACTION OF CORTISONE

The direct and indirect effects of a new discovery may be quite independent, and it is still difficult to be certain whether cortisone is going to be more important as a therapeutic weapon, as a research tool, or as the stimulus to new exploration in the search for vital information about the nature of disease. In this issue of the *Journal* we are privileged to publish this year's Heberden Oration by Dr. E. C. Kendall, the discoverer of cortisone (compound E). His paper follows in a logical sequence that of previous Heberden Orators. Hench in 1948 gave his oration on "The Potential Reversibility of Rheumatoid Arthritis"[1] only a few days after the discovery that the administration of cortisone gave remarkable relief to a patient with this disease, but he was unable at that time, as Kendall explains, for obvious and wholly admirable reasons to discuss this. In the 1950 oration Selye[2] tried to correlate these findings with his own general adaptation syndrome, although not with entire success, as he himself is the first to admit. Indeed, he refers in his latest book[3] to Pickering's criticism[4] that "the history of medicine shows how great is the tendency for a tentative and imperfectly documented hypothesis to assume the guise of so-called fundamental principles." Kendall's paper, while it may have nothing very new to tell, is an admirable review of the present position of cortisone as a therapeutic agent. That cortisone, hydrocortisone (or compound F), and A.C.T.H. will quickly relieve the symptoms of rheumatoid arthritis and of many other conditions is no longer a subject of doubt or controversy. But the problem of its practical use, particularly in chronic disease, remains one requiring prolonged investigation by experienced workers. Papers such as those of Boland[5] and Hench and his colleagues,[6] even though they describe the results of treatment for upwards of a year, are still only milestones on a long road, since patients with rheumatoid arthritis often require treatment for ten years or more. Even so, it is difficult to believe that methods will not be devised to allow practical and reasonably safe use of these hormones.

Up to the present an understanding of the aetiology of the conditions relieved by cortisone still eludes us, though the initial work seemed to follow a logical chain of reasoning. It was hoped that Selye's work might offer a solution, but unfortunately, as Professor R. G. Harrison points out elsewhere (p. 1299), some of his animal experiments have not been confirmed. Parkes and Wrigley,[7] for instance, were unable to reproduce the results of his experiments with formalin arthritis in rats. Whether or not the adrenals themselves are abnormal in rheumatoid arthritis seems doubtful. Harrison's experiments, which suggest that focal necrosis in the zona fasciculata may be related to the onset of arthritis in albino rats treated with deoxycortone, are extremely interesting, although they again pose the problem common to all animal experiments—that of deciding to what extent these results are to be applied to man. The same difficulty arises with the stimulating experiments of Long and Miles and their colleagues[8] on the effect of cortisone, A.C.T.H., thyroxine, vitamin C, and the "cabbage factor" on tuberculin hypersensitivity in guinea-pigs. Kendall himself states that, while there is no evidence as yet of a primary endocrine disorder in rheumatoid arthritis, the problem of hypersensitivity and of antibody-antigen reaction requires study. It seems that, so far as studies in man are concerned, much more precise methods to enable accurate estimations of steroids in body fluids are required, and the suggestion of Sommerville and his colleagues[9] that there may be some evidence of abnormal steroid metabolism in rheumatoid arthritis remains only tentative. Clearly these two points must be given much more intense study.

Meanwhile investigation of the treatment of rheumatoid arthritis with cortisone must continue until its practical use in chronic disease has been fully worked out. In any case, it is becoming more and more clearly recognized that the effect of cortisone is largely in suppression of symptoms rather than of the disease itself, and it is not therefore likely to replace the present well-tried methods of treatment, though it may prove a very powerful ancillary weapon. Purely experimental investigations, parallel and complementary to the clinical work, may eventually make clear the basic aetiology of rheumatoid arthritis and allied conditions, and possibly point the way to more rational and specific forms of treatment.

1 *Ann. rheum. Dis.*, 1949, **8**, 90.
2 *British Medical Journal*, 1950, **1**, 1383.
3 *First Annual Report on Stress*, 1951. Montreal, p. 4.
4 *Lancet*, 1950, **2**, 81.
5 *British Medical Journal*, 1951, **2**, 191.
6 *Proc. Mayo Clin.*, 1951, **26**.
7 *British Medical Journal*, 1951, **1**, 670.
8 *Lancet*, 1950, **1**, 492; 1951, **1**, 1085; 1951, **1**, 1392; and 1951, **2**, 902.
9 Ibid., 1950, **1**, 116.

THE NUFFIELD TRUST AND THE N.H.S.

Administrators of the National Health Service are no doubt tempted, like all State servants, to play safe, to jog along in the middle of the road which leads to mediocrity. The public, including doctors, can therefore be grateful for the independent existence of the Nuffield Provincial Hospitals Trust, which, it is clear from the report[1] published this week, intends to keep the N.H.S. under a benevolently critical eye—always with the object of improving the medical care available to the patient. The Trust's aims are not idealistic or intangible : when a question arose on what were the precise duties of a nurse, the Trust, instead of forming a committee, decided to carry out a "job analysis" of nursing. This entailed the observing and recording of every action of the nurses in 26 wards (of different kinds) for a period of eight days and nights. Over 18,000 hours of work were recorded, and the field work took over two years to complete. Incidentally, a nurse makes between 300 and 400 journeys during a spell of duty and walks 2 to 2½ miles. A similar analysis of public health nursing is at present being made. When all the material has been collected, those who have to find an answer to the original question will have facts, besides opinions, to guide them.

Another of the Trust's teams has been looking into hospital design. For many years the large open ward was favoured for hospitals in Britain. This was convenient for the nurses, but had many disadvantages, including the appearance (and often atmosphere) of an institution, lack of privacy and quiet for the seriously ill, and no barriers to cross-infection. On the other hand, the type of ward with rooms holding one to six beds ranged along a passage is costly to build and presents obvious nursing difficulties. In making its design for an experimental ward unit the team has been impressed by the evidence that "early ambulation" is now a common practice and has included a day-room for the patients who are up. Two of these experimental units are soon to be completed, one in Scotland and one in Northern Ireland. Both will consist of two 32-bed wards, containing eight single rooms and six bays with four beds in each. For ease of nursing the beds are grouped as closely as possible round the ancillary rooms. These units are to be "laboratories," not only for the testing of building materials and methods of lighting and heating, but for the reorganization of ward work generally. Here again the facts brought to light by the Trust's job analysis of a nurse's work and investigation into hospital costing should come in useful.

Another section of the report is concerned with health centres, for which the medical profession's enthusiasm is thought to be declining, perhaps due in part "to the general practitioner's individualistic preference for courteous competition," and in part to the fact that no working examples exist by which the benefits and defects of different forms of health centre can be judged. To counter this the Trust is to experiment with at least three types of health centre. The most important of these is to be at Manchester, where with the financial help of the Rockefeller Foundation the Trust is to establish a health centre "from which the general practitioners of a dense urban area will practise, where local authority clinics will be run, and where the medical school will have the opportunity both of studying social medicine and of teaching 'general practitioner' (as opposed to purely 'hospital') medicine to medical undergraduates." The general practitioners working from this health centre (their lists will be limited to 2,750 patients each) are to do two sessions a week at maternity-and-child-welfare and school-medical clinics, and one session a week as clinical assistant at a local hospital, and are to be approved as teachers by the university. As the experiment proceeds it is hoped to achieve full integration of preventive and curative services, and to build up a research unit in social medicine as well as a centre of medical education.

A special task of another experimental health centre—to be built at Corby in Northamptonshire—is to find out the kinds of treatment that can satisfactorily be given outside a hospital. Corby is a rapidly growing industrial town eight miles from the nearest hospital, and patients needing special investigations have sometimes to travel long distances. The first building will be a diagnostic health centre to be used by general practitioners and visiting consultants. Later there are to be built on the same site a maternity unit for normal confinements, a hospital unit with general-practitioner beds, and local authority clinics.

There is a suggestion here and there in this report of uneasiness about the apportionment of the patient's care—and of staff, buildings, and equipment—between three separate authorities. The Trust thinks this aspect of the National Health Service "needs constant and much deeper study than it has yet received," and, as a beginning, an experimental study is to be made in East Anglia with the object of finding out whether there is overlapping or gaps between the various authorities and whether the needs of the community,

[1] Report of the Nuffield Provincial Hospitals Trust, 1948–51. Obtainable from the offices of the Trust, 12 and 13, Mecklenburgh Square, London, W.C.1.

especially of the individual patient, are being fully met. Many of the difficulties of the N.H.S. may seem less perplexing when improved co-ordination, towards which the Trust is plainly going to strive, has resulted in a better use being made of our already enviable resources.

ANTIBIOTIC TREATMENT OF OTITIS

With the variety of chemotherapeutic and antibiotic substances now available, the choice of preparation used for an infection of the middle ear cleft does not entirely depend on the sensitivity of the invading organisms to the drug; the virulence of the organism, the resistance of the patient, the ease and comfort of administration, and the duration of the illness are other relevant factors. For mild acute infections the sulphonamide drugs retain a place because they are easy to give and seldom cause troublesome side-effects. But usually the drug of choice will be penicillin. It is highly effective in most acute infections, and the freedom from side-effects and its cheapness counterbalance the necessity for daily injections, which in children at least are often ill tolerated. The development of penicillin-resistance or infection by a naturally resistant organism requires the use of the more recently introduced antibiotics, of which two, streptomycin and chloramphenicol, are now easily obtainable in this country. Unfortunately these drugs do not share with penicillin the same freedom from side-effects. Failure of antibiotic treatment is due to resistance of the organism or to presence of dead tissue and pus, and successful treatment will then depend on the use of methods established in the pre-chemotherapeutic era.

In practice, infections of the ear can be divided into three groups: the mild acute infection seen at an early stage, the more severe acute infection, and infection due to resistant organisms or associated with dead tissue. Mild infections can be successfully treated with sulphonamides. They probably form the bulk of the cases seen in practice and rarely require more care than the general practitioner can give at home. For the more severe acute infections of the middle ear and mastoid, treatment with sulphonamides will occasionally be successful, but, when they fail, pockets of infection left smouldering in the mastoid will silently extend to cause serious complications or will flare up when the drug is discontinued. Early treatment with penicillin will cure those infections caused by sensitive organisms, but resistant organisms or dead tissue will cause failures. Acute infection due to resistant organisms is fortunately uncommon, and the incidence appears to vary in different communities and in one community from time to time. Treatment with the newer antibiotics may then be successful, but by the time the presence of a resistant organism is realized tissue destruction has often occurred and surgery will be required.

Chronic ear infections may be due simply to a resistant organism with very little retention of dead tissue. An effective antibiotic introduced into the diseased area will allow healing to take place. Recurrence may occur as a result of reinfection from persistent nasal or pharyngeal infection, lack of healing of a perforation in the tympanic membrane, or because the healed middle ear cleft has a lower resistance. In about 10% of cases of chronic otitis surgical drainage is imperative because of bone disease or cholesteatoma formation. Lewis and Gray[1] in a recent paper have described the local application of 15% chloramphenicol solution in propylene glycol in the treatment of chronic otitis. Their results bear out the principle that infection due to a sensitive organism without retained dead tissue is amenable to treatment with antibiotics. Even so, simple transmeatal treatment of granulation tissue and polyps, which may occur with a purely mucosal infection, is essential. In this series of cases, those known to have bone necrosis or cholesteatomata did not respond except when these conditions were superficial and of limited extent. The striking feature of their results was the reduction in time and effort necessary to effect a cure. Without the use of antibiotics skilled daily treatment is needed, and may have to be continued for several months. The treatment Lewis and Gray describe is successful in a matter of days—up to 21—and can be carried out by the patient with occasional supervision by the otologist. The choice of propylene glycol was decided by its ability to dissolve chloramphenicol, miscibility with water, non-toxicity, and hygroscopic properties. An ear once the site of chronic infection is more liable than a normal ear to become reinfected. It is a debatable point whether it is not wiser, when infection often recurs, to perform an epitympano-mastoidectomy and reduce the eventual loss of hearing.

A recently published report by Mr. J. I. Munro Black,[2] and an earlier paper by Moffett and Dalton,[3] describe the good results which may be obtained in acute mastoiditis in children when treated with penicillin alone. Formerly surgical drainage of the mastoid would have been necessary in all their patients. Of 118 children treated by Black, resolution without surgical intervention occurred in all the 59 cases in which subperiosteal mastoid fluctuation was absent, and in no

[1] *British Medical Journal*, 1951, 2, 939.
[2] Ibid., 1951, 2, 1191.
[3] Ibid., 1949, 2, 1087.
[4] *Lancet*, 1951, 2, 63.

fewer than 21 cases in which it was present. Of the remaining 38 cases with fluctuation, a simple (Wilde's) incision only was necessary, except in three (including one tuberculous infection), when mastoidectomy was performed. The author states, however, that three patients treated by simple incision retained a post-aural fistula for up to four weeks, and in one patient the fistula persisted for three months. Moffett and Dalton described 17 consecutive cases, of which only one required surgical drainage of the mastoid. While the avoidance of an operation may be desirable, the preservation of hearing is the ultimate goal. The longer infection persists in the middle ear or mastoid the greater the eventual loss of hearing from damage to the tympanic membrane and limitation of ossicular movement by scarring. The Schwartze mastoidectomy is a simple operation, and with modern anaesthetic technique causes little or no greater systemic disturbance than Wilde's incision. The risks of the operation when performed by a trained otologist are slight. and healing is rapid. Many otologists believe that Wilde's incision is seldom called for, and that a Schwartze operation is indicated as soon as it is apparent that antibiotic treatment alone will be prolonged or unsuccessful. Acute mastoiditis with subperiosteal abscess in adults will usually require mastoidectomy; the results of treatment with antibiotics alone cannot be expected to be so effective as in children because of the greater vascularity of the growing temporal bone. McKenzie[4] had to perform a Schwartze mastoidectomy on 12 out of 161 patients of all ages admitted to hospital with acute suppurative otitis media. Although intracranial complications are rare, in his opinion the need for mastoidectomy is unlikely to be less in the future than it is at present. The true value of the new antibiotics lies in their ability to prevent spread of infection until surgery can eradicate the focus.

There is every reason to hope that increasing knowledge of the use and limitations of the antibiotics will reduce the incidence of chronic ear disease and the deafness that it causes. Surgery for infective disease of the temporal bone will then be more often performed for the saving of hearing than for the saving of life.

GLUTATHIONE

There has recently been a revival of interest in the compound glutathione, particularly in its changing level in the blood in cases of diabetes. Glutathione was discovered by Hopkins in 1921, and was later shown to be a tripeptide formed from glutamic acid, cysteine, and glycine. Two molecules may become linked by oxidation (2 G–SH ⇌ G–S–S–G), but the term "glutathione" usually signifies the reduced form. It occurs in the red blood cells and in other tissues, particularly the liver, but little definite is known concerning its function, despite extensive investigation.

X-irradiation produces in experimental animals an eventual fall in blood glutathione, and glutathione treatment assists the recovery of such animals.[1] There are reports that the liver glutathione level is high in rats bearing sarcomata[2] and low in rats with necrosis of the liver.[3] Other reports deal with conditions as diverse as cataract,[4] sickle cell anaemia,[5] and polyarthritis.[6] Diabetes produced by alloxan in animals,[7] or by A.C.T.H. in susceptible humans,[8] is associated with a fall in the blood glutathione level, and can be prevented or mitigated by intravenous injection of large doses of glutathione. In patients with diabetes mellitus, however, blood glutathione determinations have not consistently given low values, at least in the absence of ketosis.[7 9 10] By methods more specific than those used by some investigators, Binkley and collaborators[11] have obtained evidence for a diminished level of glutathione in the blood of human diabetics, associated with a rise in the level of a glutathione derivative tentatively identified as γ-glutamyl cysteine.

In discussing the function of glutathione, Binkley[11] points out that little is known of the metabolism of glutathione itself. He suggests that it is formed in the liver—which would account for the fall in blood glutathione in patients with acute hepatic disease—and is transported to certain other tissues, notably the kidney and intestine; in such tissues it may be broken down by specific enzymes to give derivatives such as γ-glutamyl cysteine. It is evident, then, that caution should be exercised in interpreting any findings based only on determinations of blood glutathione.

It was originally thought that the function of glutathione was to take part in oxidative processes by acting as a hydrogen carrier; but this idea, although recently supported by experiments with plant tissue preparations,[12] is at present rather out of favour.[13] Emphasis is now placed primarily on the capacity of glutathione to maintain in the reduced state certain enzymes which are inactivated if their sulphydryl (–SH) groups become oxidized.[13] It is on these lines that explanations have been sought for the effects of *x*-irradiation,[1 13] alloxan,[7] and A.C.T.H.[8] In the case of

1 Cronkite, E. P., Brecher, G., and Chapman, W. H., *Proc. Soc. exp. Biol. Med.*, 1951, **76**, 396; Peterson, R. D., Beatty, C. A., and West, E. S., ibid, **77**, 747.
2 Meduski, J. W., *Brit. J. Cancer*, 1949, **3**, 559
3 Lindan, O., and Work, E., *Biochem. J.*, 1951, **48**, xxxi.
4 Kinsey, V. E., and Merriam, F. C., *Arch. Ophthal., Chicago*, 1950, **44**, 370.
5 Stetson, T. L., and Chandler, A., *Bull Johns Hopk. Hosp.*, 1948, **83**, 176.
6 Kuzell, W. C., Gardner, G. M., Fairley, de L. M., and Tabar, P. S., *Stanford Med. Bull.*, 1950, **8**, 83.
7 Lazarow, A., *Physiol Rev.*, 1949, **29**, 48.
8 Conn, J. W., Louis, L. H., and Johnston, M. W., *J. Lab. clin. Med.*, 1949, **34**, 255; idem, *Science, Balt.*, 1949, **109**, 279; Hess, W. C., Kyle, L. H., and Doolan, P. D., *Proc. Soc. exp. Biol. Med.*, 1951, **76**, 418; Kass, E. H., Ingbar, S. N., and Finland, M., ibid., 1950, **73**, 669.
9 Caren, R., and Carne, H. O., *Amer. J. Sci.*, 1951, **221**, 307.
10 Illing, E. K. B., Gray, C. H., and Lawrence, R. D., *Biochem. J.*, 1951, **48**, 637
11 Binkley, F., Christensen, G. M., and Wu, F. C., *J. biol. Chem.*, 1951, **192**, 29; Binkley, F., *Nature, Lond.*, 1951, **167**, 888.
12 Mapson, L. W., and Goddard, D. R., *Biochem. J.*, 1951, **49**, 592; Conn, E. E., and Vennesland, B., *J. biol. Chem.*, 1951, **192**, 17.
13 Barron, E. S. G., *Advances in Enzymology*, 1951, **11**, 201.
14 Ingbar, S. H., Otto, J. F., and Kass, E. H., *Proc. Soc. exp. Biol. Med.*, 1951, **77**, 20
15 Griffiths, M., *J. biol. Chem.*, 1950, **184**, 289.
16 Lazarow, A., *Proc. Soc. exp. Biol. Med.*, 1950, **74**, 702.
17 Hanes, C. S., Hird, F. J. R., and Isherwood, F. O., *Nature, Lond.*, 1950, **166**, 288.
18 Lohmann, K., *Biochem. Z.*, 1932, **254**, 332.

experimental diabetes it is postulated that impairment of the insulin-producing mechanism is largely a consequence of a fall in the glutathione content of the β-cells, the capacity of which to produce insulin is assumed to depend on the maintenance of certain enzymes in the reduced form. In addition, or perhaps alternatively, there may be a similar change in the kidney tubules, the ability of which to reabsorb glucose might be impaired if enzyme sulphydryl groups become oxidized.[14] Depletion of glutathione in the tissues could be produced by alloxan itself,[7] or by a related compound such as uric acid; the latter is known to be elevated in the blood of humans made diabetic by A.C.T.H.[8] and is itself diabetogenic in animals kept on a sulphur-deficient diet.[15]

That these theories should be treated with reserve is emphasized by the observation of Lazarow[16] that glutathione may enhance, rather than reduce, the diabetogenic action of cortisone in the force-fed rat. It may also be pointed out that there is some disagreement about the effect on glutathione levels of insulin[9 11] or of A.C.T.H.,[8 11 14] and that inadequate attention has been paid to the possible occurrence of species differences.

If the onset of diabetes is indeed conditioned by the level of glutathione in certain tissues, it cannot be assumed that the role of glutathione is solely to preserve the sulphydryl groups of certain enzymes from oxidation. In discussing the possible importance of glutathione in absorptive processes, and in the maintenance of the ionic environment of cells, Binkley[11] directs attention to the possible participation of the labile glutamyl portion of the glutathione molecule. This aspect has also been studied by Hanes and collaborators,[17] who consider, however, that glutathione may be concerned in protein synthesis, since its glutamyl radical may become detached and linked to another amino-acid ("transpeptidation"). It is conceivable, too, that glutathione plays a role in carbohydrate metabolism, since the function of the enzyme glyoxalase is dependent on its presence.[18] It has also been suggested that glutathione may be specifically concerned in haematopoiesis.[1 13] But at present it is not possible to give an integrated account of the metabolic function or functions of glutathione, or to evaluate satisfactorily the numerous experimental and clinical observations relating to glutathione.

DIAGNOSIS BY HEART PUNCTURE

The technique of heart puncture in man for the visualization with diodrast of the ventricles and great vessels by Ponsdomenech and Núñez[1] may arouse much adverse criticism. Yet cardiac puncture in man is not a new procedure: it was employed in 1930 by Baumann[2] for obtaining samples of mixed venous blood to check the respiratory method of cardiac output estimation; more recently Buchbinder and Katz[3] punctured cardiac chambers through the chest wall to obtain direct pressure records, and Hesse and Minkus[4] used the method on themselves to study ventricular movements. Workers in this country have also performed heart puncture, though the series have been small. Previously regarded with disapproval as a research procedure, the Cuban authors now advocate it as a diagnostic method. They employ a technique resembling that of Marfan for paracentesis of the pericardium, introducing a trochar into the right ventricle through its inferior surface, and into the left by crossing the interventricular septum in its lowest part. Important coronary vessels are avoided by using this route. Ventricular extrasystoles are frequent at the moment of puncture; but their occurrence is also frequent during catheterization of the right ventricle. At the time of publication 56 heart punctures had been performed without mortality or untoward incident. Diodrast for visualization was injected, using the Don Santos apparatus. In one case the dye was injected into the pericardium because the trochar had been introduced too deeply. The injection of diodrast itself must increase the hazard of the procedure, since it may produce profound effects on the circulation; the blood pressure falls, often to low levels,[5] and abnormal rhythms and electrocardiographic changes suggestive of myocardial anoxia may develop.[6 7]

It seems unlikely at present that the method will come into widespread use. It may, however, prove of anatomical value in certain cases where clear visualization is not obtained by the usual method of angiocardiography—as, for example, in the presence of a large interatrial communication—and might replace retrograde aortography in coarctation of the aorta. The physiological value of the procedure in its present form is undoubtedly more limited. Intraventricular pressure records were obtained in one case in the series under discussion, but the anaesthesia which the authors have found it necessary to employ must affect the interpretation of such records. Further experience with the method may perhaps in the future grant it recognition as a diagnostic tool and bring it into line with the now respectable techniques of cardiac catheterization and angiocardiography.

1 *Amer. Heart J.*, 1951, **41**, 643.
2 *Z. klin. Med.*, 1930, **115**, 41.
3 *Proc. Soc. exp. Biol., N.Y.*, 1949, **71**, 673.
4 *Z. KreislForsch.*, 1949, **38**, 613.
5 Howarth, S., *British Medical Journal*, 1950, **2**, 1090.
6 Zinn, W. J., Levinson, D. C., Johns, V., and Griffith, G. C., *Circulation*, 1951, **3**, 658.
7 Horger, E. L., Dotter, C. T., and Steinberg, I., *Amer. Heart J.*, 1951, **41**, 651.

CARDIOVASCULAR DISEASE IN COTTON WORKERS

The Registrar-General has recorded high death rates from cardiovascular disease among cotton workers since 1891; despite this there has never been any clinical evidence that cotton workers were particularly prone to such diseases. In contrast, clinical interest has

8 Hill, A. Bradford. Industrial Health Research Board Report No. 59, 1930, H.M.S.O., London.
9 Harvey, P. N. Report of Departmental Committee on Compensation for Card-Room Workers, 1939, H.M.S.O., London.
10 *Brit. J. industr. Med.*, 1951, **8**, 77.
11 *British Medical Journal*, 1947, **2**, 771.

been centred on the susceptibility of cotton workers to respiratory disease,[8 9] and byssinosis, a form of progressive asthma, has been recognized as being a specific industrial risk of the cotton industry. The question arises, therefore, whether the high death rate from cardiovascular disease is real or whether it can be attributed to a confusion between deaths from cardiac and deaths from respiratory causes.

Since 1920 practitioners have been entering multiple causes of death on death certificates with increasing frequency, and the methods used by the Registrar-General for allocating such cases to one or other heading, prior to 1939, seriously exaggerated cardiovascular mortality at the expense of respiratory mortality. Thus methods of statistical book-keeping can be held to account for much of the excess cardiovascular mortality attributed to cotton workers at the time of the 1931 census. Schilling and Goodman[10] have made a detailed study of the available evidence (as a prelude to a clinical investigation) and have concluded that part of the excess cardiovascular mortality should be considered to be real. They found, for example, that the excess mortality is greatest among strippers and grinders, the occupational groups most exposed to cotton dust, and that this remains true after making an estimated allowance for misclassification. Further, they found an unexpectedly large number of deaths in the same group from cerebral vascular lesions, which is certainly to be expected if cotton workers have any increased liability to hypertension.

Others allow that cotton workers have a high mortality from such conditions as hypertension, but deny that it is due to their occupation. Platt[11] has suggested that a high incidence of hypertension could be explained by the operation of hereditary factors in the comparatively inbred population of the Lancashire cotton towns; he pointed out that the Registrar-General does, in fact, record a high mortality from cardiovascular disease throughout the whole of Lancashire and Cheshire. The geographical factor is not, however, sufficient to account for all the excess mortality among cotton workers. The close relation observed between the degree of exposure to dust and the death rate from cardiovascular disease within the cotton trade points strongly to the existence of an occupational factor, and its elucidation may throw light on the aetiology of hypertension.

FAMILY PROGNOSIS IN EPILEPSY

For many hundreds of years public opinion has held that epilepsy is strongly inherited. Lennox[1] quotes Burton's statement in *The Anatomy of Melancholy* that the ancient Scots castrated epileptics; in National Socialist Germany idiopathic epilepsy was one of the grounds for compulsory sterilization. In many American states it is illegal for idiopathic epileptics to marry, and this is also the law in Sweden unless they undergo sterilization,[2] though in the U.S.A. the laws are moribund and in Sweden are seldom applied. One would naturally suppose from this that the near relatives, and particularly the children of epileptics, are often themselves affected. Not only is this not the case, but some authorities even doubt whether the near relatives of the general run of epileptics are more often affected than one would expect by chance—though in certain individual families epileptic attacks are undoubtedly symptoms of an inherited disease entity (for example, in myoclonus epilepsy).

There are obviously great difficulties in the genetic analysis of a condition such as epilepsy, especially difficulties in diagnosis and classification. Idiopathic epilepsy can be diagnosed only by exclusion, and the more thorough the investigation with modern techniques the more frequently are focal lesions found causing the epilepsy. Lennox holds that his own twin studies and those of Conrad suggest that idiopathic epilepsy is largely determined genetically. Unfortunately, there is some evidence of bias in the selection of both these series, but even so the findings are important. However, the investigations of near relations other than identical twins of epileptics show that only a small proportion are affected. Lennox and Alström[2] have both reported large series; Alström's series has some advantages: he investigated all the families himself, he shows the incidence in each degree of relationship separately (whereas Lennox only gives figures for all first-degree relatives taken together), and he has made careful allowance by Strömgren's weighting method for the possibility that younger relatives have yet to develop epilepsy. Lennox found the incidence of epilepsy in first-degree relatives to be about 3%. Alström found the same incidence in the children of his index cases (3±0.93%), but a rather lower incidence in sibs (1.5±0.25%) and parents (1.3±0.27%). These figures must be compared with those in the general population. The percentage of men drafted for the American armed Services with epilepsy is approximately 0.5%. Many of these are young men who will develop epilepsy later, and Alström finds that at the age of 21 the incidence of epilepsy in brothers and sons would be about 0.9%, not significantly different from that in the American draftees. Lennox, but not Alström, found a markedly higher incidence in the near relatives of patients with idiopathic epilepsy (or, as Alström calls it, epilepsy "of unknown cause"). Probably further genetic analysis should wait till the differentiation of the conditions which can cause the symptom of epilepsy is more complete. In spite of our ignorance, however, the epileptic who wants to know the chances that a child of his or hers will be affected can be given the reassuring empirical figure of about 1 in 30, unless the family history suggests that in this particular instance the epilepsy is more strongly inherited. This will probably not deter the would-be parent from having at any rate a small family; but if the epilepsy is accompanied by mental deterioration, or if a woman who is epileptic would be greatly handicapped in caring for babies, reproduction might well be inadvisable for social reasons.

[1] *J. Amer. med. Ass.*, 1951, **146**, 529.
[2] *Acta psychiat., Kbh., Suppl.* 63, 1950.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

PRINCIPLES OF PHYSICAL MEDICINE.—I. REMEDIAL EXERCISES

BY

BASIL KIERNANDER, M.B., M.R.C.P., D.M.R.E., D.Phys.Med.

Director, Department of Physical Medicine, Hospital for Sick Children, Great Ormond Street

Remedial exercises have an important place in general practice, as there is now an increasing tendency for the *active* rehabilitation of patients. It is an advantage, therefore, if the general practitioner can advise his patients on what are appropriate exercises for them to perform.

A great deal of time can be saved in convalescence by correct rehabilitation. The day when passive physiotherapy was the mainstay of treatment has passed, and active exercises are now regarded as much the most important part of rehabilitation; other methods are only ancillary. This must be impressed on the patient at all times. He must be made to learn that by his own efforts he can return to normality, and that the onus of doing so lies largely on his own shoulders; the part of the physiotherapist is only to supervise and teach the appropriate exercises, under the direction of the medical practitioner. The slogan of a successful physiotherapy department should be "active movements of the mind and body of the right sort at the right moment," and this is particularly applicable to the cases dealt with by the general practitioner. I have included the expression of "mind and body" in that order intentionally, as a correct attitude to recovery is even more important than the carrying out of exercises.

Prevention and Treatment of Postural Deformity

Patients with postural errors may be grouped into those without any structural defects and those with associated structural alterations. The first group includes patients with postural errors which have been detected at medical examinations. They often occur in schoolchildren, who should have no symptoms from them. These errors of posture may be either static or dynamic.

Static errors are those that are apparent when the patient is stationary, either sitting or standing. Some of the commonest errors of this type are spinal (for example, early scoliosis), others are peripheral (for example, pes planus and valgus ankles). In this type of case it is a good plan, if the children are attending a school where physical training is given, to arrange for the instructor to include simple remedial exercises in the gymnastic period—most instructors have the necessary experience. The instructor can watch the posture of the children and remind them to hold themselves correctly. It is uncommon to find one of these postural errors by itself; usually there will be a variety of small errors and hence the whole posture must be corrected. Details of appropriate exercises are given in the Appendix.

In children remedial gymnastics have to be varied according to age. In infancy, before the child's co-operation can be obtained, it is quite a specialized task to work out a programme of gymnastics depending entirely on reflex movements, and it is advisable to have the assistance of a physiotherapist experienced in paediatric work. When the child is over 1 year or 18 months he may be encouraged to do the right exercises by the use of simple play movements, and this will continue until much later in childhood, when he will be able to co-operate voluntarily in his exercises. It is always important to see that the remedial exercises are interesting enough for the patient; they can be varied in detail from time to time. With children it is especially important that the parents should be taught how to supervise the exercises, as these must be carried out for at least half an hour each day.

The dynamic postural errors are those in which movement is not as good as it should be. This group includes errors of respiration—for example, very poor lower-costal movement and "up and down" breathing—and errors in gait and co-ordination. A programme of re-educational exercises will correct these errors.

If errors of posture are neglected and structural deformities develop, remedial exercises will be of value in treatment in addition to any other orthopaedic measures that may be necessary. Although in these cases the localized programme of exercises is important, it must be part of a generalized programme to restore good posture and normal movement to the whole body.

The Bedridden and the Aged

For patients lying in bed exercises will prevent loss of muscle tone and wasting, and the development of deformities of the joints. Hence, in bedridden patients a general series of exercises should be carried out (see Appendix), within the limitations of their particular disabilities. Breathing exercises are important in preventing pulmonary collapse and hypostatic bronchopneumonia, and are specially useful in surgical patients, particularly before operations on the chest or upper abdomen.

Every effort should be made to keep elderly people active for as long as possible. If practicable, they should be kept moving about and should not be allowed to become bedridden until deterioration of their health leaves no alternative. In those who have become bedridden a programme of exercises designed to keep their joints mobile and their muscles in good tone not only keeps them alive longer but makes them very much happier. In addition to exercises, various forms of occupational therapy can be recommended. There is a wide range of different kinds of handiwork from which to choose; some will find more interest in needlework, some in leather work, others in simple carpentry, for instance. So far as is possible occupational therapy should be productive work, as that offers an incentive of interest to the patient.

Rehabilitation of the Injured

Remedial exercises are essential to the restoration of function after any injury. In minor injuries without damage to bone, active movements should be encouraged from the start to prevent loss of function. In most

sprains and strains exercises are required to keep the affected part mobile; in addition, supervision is necessary to ensure that no functional error such as a limp develops. If a joint has been injured and there is a traumatic effusion, the affected joint must be rested, but it is important that the muscles of the limb should be kept in adequate tone. For instance, quadriceps contractions should be introduced early in traumatic synovitis of the knee, as the quadriceps, especially the vastus internus, may start to lose tone and waste within 24 hours of the injury. A simple exercise such as bracing the knee back can be carried out many hundreds of times during the course of the day without disturbing the patient.

Again, if the bones have been fractured, remedial exercises should be started early, once the fracture has been reduced and the bones splinted. The aim of such exercises is to maintain the mobility of the rest of the patient's body and of the damaged limb, without disturbing the position of the bony fragments. A particularly important example of this is the maintenance of shoulder movement in patients with fractures of the forearm; shoulder exercises to maintain all movements, especially abduction, should be carried out from the beginning. The rest of the body should be kept in good tone, and mobility maintained, by a generalized programme of exercises.

Once the fracture has united and there is no longer any need for splinting, exercises to restore the full function of the injured part are instituted. In treating injuries it is of special importance to prevent the formation of adhesions. In many cases of sprained ankle for example, if mobility is not introduced early, restriction of movements soon develops.

Exercises for Asthma and Bronchitis

The aim of exercises for the asthmatic patient is to teach relaxation and to give re-education in breathing. He holds his chest tense, and it becomes more difficult to teach him to relax as his age advances. It is, however, of the greatest benefit to him if he can relax properly, for when an attack starts he will then be able to lessen his discomfort. He has an "up and down" type of respiration, and hardly uses his lower intercostal muscles. He should therefore be taught lower-costal and diaphragmatic breathing. As with all breathing exercises, he should practise these to such an extent that they cease to be exercises and become his normal breathing. The shoulder-girdle and the thorax of asthmatics have a tendency to lose their mobility; in particular, the mid-dorsal spine becomes almost rigid after asthma of long duration. A programme of exercises to mobilize the dorsal spine and shoulder-girdle should be instituted, including exercises to mobilize the costovertebral joints. For details of exercises for asthmatics see the Appendix.

Patients with chronic bronchitis almost invariably have minimal lower-costal movement, and the first object should be to teach them the proper use of these muscles. In long-standing cases postural drainage over the edge of the bed or couch should be instituted for 20 to 30 minutes twice a day; drainage can be helped by the physiatherapist "tipping and clapping" the chest. Patients with bronchiectasis will require chiefly postural drainage, which must be planned so that the affected part of the lung is adequately drained (for details see Pye's *Surgical Handicraft*); exercises to develop the movement of the affected lung should be included in the general breathing exercises. The same applies to the post-operative treatment of pulmonary abscesses and to any other post-operative chest condition in which respiratory function should be restored.

The Rheumatic Diseases

In addition to the general and specific treatment in articular rheumatism, it is most important to maintain mobility of the affected joints. In osteoarthritis of the shoulders, hips, and knees in elderly people there is a great tendency for the patient to rest the affected joint, and thus relieve the pain which is so marked on movement. This results in limitation of movement or even in ankylosis of the joint. To combat this a careful programme of exercises should be devised so as to maintain the full range of movement of the affected joints. Where restriction of movement is already evident, restoration of function must be attempted by remedial exercises, helped where needed by manipulation. Exercises are a simple way of stretching and breaking down adhesions without undue discomfort or difficulty.

In osteoarthritis of the cervical spine pain can be greatly relieved by neck-stretching exercises. The patient with osteoarthritis of the hip and knee must be taught to walk correctly in order to prevent him developing a limp, and to avoid weight-bearing on the most painful part of the articular surface of his knee or hip. Trick movements may have to be taught to compensate for permanent loss of movement of a joint.

Non-articular rheumatism is a frequent problem in general practice, and it is important to stress that physiotherapy in the form of remedial exercises, helped by massage and heat, is the most successful treatment for this group of disorders. It is important to maintain good muscle tone throughout the body, as fibrositic nodules appear much more often in muscles which are atonic. The high incidence of painful fibrositic nodules in the back muscles of athletic people in middle age is accounted for to a large degree by lack of exercise. Remedial exercises, therefore, have a part to play in reducing the occurrence of such nodules. When massage, heat, or injections are used to relieve fibrositis, the patient should be given a programme of exercises which should be carried out for a quarter of an hour each day (see Appendix).

Neurological Conditions

Re-educational exercises are of great value in the group of congenital deformities classified together as "cerebral palsies." Exercises have been designed for teaching walking and other movements, including feeding and domestic functions of all kinds, but parents must understand the aim of the exercises and be shown how to supervise them at home. The programme will vary according to the clinical condition; the approach, of course, being entirely different in, say a child with athetosis from that in one who is spastic. The teaching of relaxation and voluntary control of tremor is also important in these cases; a specialized programme of exercises to improve co-ordination should also be included. Trick movements may have to be taught to those for whom normal movements are impossible.

The largest group of patients with acquired neurological disease calling for remedial exercises is formed of those with anterior poliomyelitis, in whom muscular re-education should be instituted as soon as the acute stage of the disease is over (see Kidd's *Physical Treatment of Anterior Poliomyelitis*). The usual practice is to chart the voluntary movements and electrical reactions of all the skeletal muscles in the body immediately after the acute stage, and then to plan a progressive programme of muscle re-education on the basis of these results. For paralysed muscles the exercises will have to be graded according to the degree of function present. In the early stages the muscles generally have to be assisted either manually by the physiotherapist or by appropriate slings or pulleys, but as their strength returns exercises in the gymnasium and, finally, active movements against resistance are employed. This whole programme is much easier if the early exercises can be performed in a swimming-pool.

Much can be done by exercises in cerebral vascular disease and after spinal injuries to keep those with paralysis on the move and thus save them from becoming bedridden. In tabes and other conditions in which co-ordination is poor, Frenkel's exercises can be used; these teach the patient to develop a reasonable gait and movement of the lower limbs. (For details of suitable exercises see Kern's *Physical Treatment of Injuries of the Brain and Allied Nervous Disorders.*)

Obstetric Cases

While this is still a rather controversial field, I consider that antenatal and post-natal exercises can be of great value. Antenatal exercises should be introduced when the pregnant mother first attends an antenatal clinic early in her pregnancy. The exercises are planned to teach her voluntary control over the movements of her abdominal and pelvic muscles, so that when labour starts she can co-operate with the midwife by voluntarily contracting the appropriate muscles during her pains, and then relaxing. Exercises to improve the tone of the abdominal muscles will tend to prevent an unduly lax abdomen after labour. Incorporated in this programme of antenatal exercises are some to mobilize the lumbar spine and pelvis. (For details see Randall's *Training for Childbirth.*) Once the patient is in bed for her confinement, she should continue with these exercises.

Post-natal exercises carry on the good work started in the antenatal period, and their primary aim is to restore the muscle tone of the abdominal wall and pelvic floor, and also the general posture. If these exercises are carried out conscientiously every day in hospital or at home the incidence of post-natal backache can be much diminished. These exercises also play an important part in restoring the abdominal contour.

Massage

The role of massage as an ancillary procedure to remedial exercises is fairly limited. It can be used to reduce oedema mechanically when this is indicated—for example, after any injury or thrombosis—by promoting better venous and lymphatic drainage. Massage has a special place in the treatment of non-articular rheumatism, particularly if fibrositic nodules are present, and it helps relaxation if there is muscle spasm, as in lumbago or after injuries when painful limbs are mobilized.

APPENDIX: SOME USEFUL REMEDIAL EXERCISES

Postural Scoliosis

Any cases with major postural defects, especially of the spine, should be referred for specialist advice, but the following table of basic exercises will be useful in treatment.

The aim is to eradicate the faulty postural sense and to replace it by a normal one. The treatment is long and needs the intelligent co-operation of the patient (this can be obtained in quite young children). It is mentally and physically tiring. While it is necessary to move as rapidly as possible through the various stages, care must be taken not to pass on until each stage has been mastered. Through all stages of treatment the patient should be undressed so that the whole of the body and limbs can be observed.

First Phase.—This consists in teaching the correct lying position, first on the back, later on the face. The patient is placed in position and is then corrected by verbal instructions. The following points must be observed: (1) Feet against the wall in a normal position, and the patient feeling as if he is elongating the whole of the body. (2) Muscles of legs braced. (3) Abdominal and gluteal muscles contracted to hold the pelvis straight—that is, no lordosis. (4) The patient must not hold his breath but breathe freely. (5) Shoulders level and in line with the iliac crests and relaxed. Arms lying naturally by the sides of the body. (6) Neck in midline of shoulders, with the chin over the sternal notch. (7) Ears level. (8) Chin in when the patient tries to eliminate the cervical curve, thus getting the feeling of stretching out. When this position has been learnt, add simple arm, leg, head, and trunk movements, taking care that the starting position is held correctly.

Second Phase.—Teach correct sitting position on a stool. Correct verbally. Later the position should be assumed automatically. The following points must be observed: (1) Feet held in normal position, with the foot at right angles to the leg. (2) Legs at right angles to the thighs. (3) Whole of thighs supported on stool. (4) Trunk erect. (5) Shoulders level, not braced back. Arms hanging naturally. (6) Neck in midline. (7) Ears level. (8) Chin in, as previously described. Add simple head, arm, leg, and trunk movements. Again the starting position must be maintained correctly.

Third Phase.—Teach the correct standing position. This is much more difficult than the previous positions, as more joints are required to hold the position. (1) Standing erect, with feet apart. (2) Feet, with arches lifted, facing forwards along a straight line. (3) Pelvis controlled by abdominal and gluteal muscles. (4) Shoulders level over pelvis, relaxed. Arms hanging naturally. (5) Head balanced on shoulders as previously described. As before, add arm, leg, trunk, and head movements, progressing to a programme of vigorous gymnastic exercises.

Lordosis

1. Lying on the back in bed with knees bent and feet on the bed, lift both knees on to the chest and lower slowly, making quite sure that the whole of the back touches the bed and there is no hollowing in the lumbar spine.

2. Standing with feet apart and hands on hips, contract the abdominal and gluteal muscles so that the pelvis is tipped, thereby eliminating the lumbar curve. Great care must be taken that the upper trunk does not move.

Kyphosis

1. Sitting with legs straight out in front (or with the knees bent and feet on the floor, or with the legs crossed), elbows bent, fingers resting on the shoulders, and arms tucked into side, lift the arms forwards, upwards, backwards, and downwards, so that the contraction of the muscles between the shoulder blades and the stretching of the pectoral muscles can be felt.

2. Lying on the face, hands by the side, turn the palms of the hands outwards so that the elbows point inwards. This should produce a strong contraction between the shoulder blades. The exercise is then made harder by the head and shoulders being raised. (The chin should be well tucked in and only the shoulders and head raised; if more movement is allowed to occur, a lordosis will be produced.)

Flat-feet in Children

The objects are to strengthen all the muscles of the feet and to teach agility and spring. For this the following exercises should be practised daily: (1) picking up marbles with the toes; (2) writing on the floor with the big toe; (3) walking on tip-toe; (4) all simple dancing steps in which the toes are pointed; (5) all games in which the child is alternately standing on the toes and changing to ordinary standing; (6) walking up an incline; and (7) climbing with bare feet.

Flat-feet in Adults

The objects are to loosen the stiff joints, strengthen the weakened muscles, and restore co-ordination between the muscle groups. Each is important, and one should not take precedence over the other. If the joints are loosened before the muscles are strong enough, more pain will be produced.

The patient should learn to stretch and loosen all the joints in the feet. He should try to mould the foot as near the normal as possible with his hands. (1) With the feet on the floor and at right angles to the legs, attempt to move the big toe away from the remaining four. (2) Spread the toes apart and relax. (3) Lift the transverse arch, without shortening the foot. The object is to exercise the lumbrical muscles. Care must be taken to avoid raising the arch by other muscles.

When these intrinsic muscles have been strengthened, give exercises and movements that will help co-ordination and quickness of action, such as skipping, walking along a chalk line, walking with a bouncing action using all the muscles of the feet and legs, and standing correctly with feet facing forward and ankles maintained in a corrected position.

The Bedridden Case

The bedridden patient should be encouraged to move freely about the bed. He should help himself on and off the bed-pan, and attempt to feed and wash himself and to do his own hair. He should move his legs and feet about many times during the day: the bedclothes must therefore be light and not weighed down. The following exercises should be performed twice daily.

1. Lying flat in the bed with a very small pillow under the head and the bedclothes removed except for a very light blanket, straighten the whole of the body, contracting as strongly as possible the buttock muscles, abdominal muscles, and all the leg muscles, the feet being held at a right angle. Then relax completely and repeat the whole performance several times. Finally, lie on alternate sides, again straightening the whole of the body, especially the hips and the back.

2. Sitting comfortably with the back well supported and a small pillow under the knees, drop the head forward and back four or five times (or more if capable); then turn the head to the right and left four or five times. Get the maximum amount of movement, stretching all the muscles round the neck.

3. Sitting as above, lift the arms up over the head, out to the side, and down. Repeat four or five times, or more often.

4. Sitting as above, bend and stretch the arms vigorously in all directions five to ten times.

5. Sitting as above, bend and stretch the fingers ten times. With the hands clenched, bend and stretch the wrists ten times.

6. Sitting as above, bend and stretch first one leg and then the other. If possible, do this in the lying position.

7. Sitting as above, point the toes down, then turn the foot in, then pull the foot up as far as possible. Repeat the performance several times. This should be done quickly and vigorously.

8. Breathe deeply in and out, trying particularly to move the lower ribs and also the back of the ribs where they rest on the pillows. These breathing exercises can be assisted if the instructor's hands are placed on the part of the ribs where movement is needed, gentle pressure being exerted on breathing out. The hands remain in position when the patient breathes in, this indicating where movement is required.

9. Move the trunk in all directions, especially turning as far round to the left and right side as possible. Bend the back backwards to counteract the tendency to forward flexion of the spine.

Daily General Exercises for Improving Physique after Fibrositis

1. Standing with the feet apart and the body held erect, fingers touching the shoulders, elbows bent, arms touching the side of the body, bend the arms vigorously upwards, forwards, sideways, and down, returning to the starting position after each movement.

2. Standing with the feet apart and the hands on the hips, move the head forwards and backwards.

3. Standing as above, lift the heels and bend the knees as far as possible, keeping the trunk absolutely upright; straighten the knees and lower the heels.

4. Standing with the feet apart and the arms hanging loosely, drop the trunk forwards, rotate to the right, arch backwards; rotate to the left, drop forwards, and return to the starting position.

Exercises for Asthmatics

Relaxation.—Lie on the bed with the feet resting on the bed and the knees bent and the head slightly raised on a pillow. Aim to get complete relaxation of shoulders, arms, hands, and thorax, especially the upper part of it. This needs concentration by the patient and is not easy to do. Also this should be taught with the patient lying on the side, with the knees bent and the head bent forward to relax the thorax. The patient breathes out and takes a small breath in, using the lower thoracic region. If the patient can acquire the art of relaxing and correct breathing, asthmatic attacks can be prevented or considerably lessened.

Breathing Exercises.—(1) The patient lies on his back with the feet on the bed and the knees bent, and relaxes as explained above. He breathes out, first collapsing the upper costal region, then the middle region, and finally the lower, contracting the abdominal muscles to expel the utmost amount of air. On breathing in, the upper parts of the abdominal muscles should be relaxed and the diaphragm contracted. The upper region of the thorax should not move and the shoulder and neck region should remain relaxed. (2) Lying in the position described above, the patient breathes out as before, but, on breathing in, the lower ribs should be expanded. This can be assisted if the hands are placed over the lower ribs and slight resistance given as the patient breathes in. The resistance should not be too great, otherwise it will defeat its object. (3) When the patient is proficient in these exercises, the two should be combined, so that the lower ribs and the diaphragm act together.

Mobilizing Exercises.—(1) The thorax is often very stiff and must be loosened before effective breathing can be taught. With the patient in a correct sitting position, the trunk should be turned quickly and vigorously many times in the following directions: forward; backward, splaying out the lower ribs; sideways (this is not a big movement; the patient "tucks in" the ribs on the bending side, keeping the legs and pelvis in a good position); and rotation to alternate sides (again the legs and pelvis must be held in the correct position). (2) The shoulder-girdle will also require mobilizing. In the sitting position, lift the shoulders up towards the ears and then let the shoulders drop (the downward movement is the more important). Sitting, move the clavicles forwards and backwards. With the arms bent and the finger-tips touching the shoulders, move the elbows forwards, upwards, backwards, and downwards.

SPEED AND HUMAN ADAPTATION

HUNTERIAN SOCIETY DEBATE

The Hunterian Society staged its annual debate at the Apothecaries Hall on November 12 when, under the chairmanship of Sir ARTHUR PORRITT, the proposition was argued, "That the age of speed has outrun human adaptation."

An Age Without Leisure

Dr. MACDONALD CRITCHLEY considered that there could be no doubt about the proposition's validity. If a succession of stimuli were given too quickly the nervous system failed to respond or responded in an abnormal manner, It was not the mere fact that it was possible to travel at 200 miles an hour which constituted the menace; it was the restless turmoil of incessant, noisy, compulsive activity which was at the base of our nervous dilapidation. This restlessness was undoing the good which preventive medicine had slowly and laboriously striven to bring to mankind. Of what avail was it to extend the expectation of life, to conquer infectious disease, to improve surgical technique, if nervous disorders—neuroses, psychoses—became more rife? We were building up a population of elderly hypochondriacs who simply would not fade away. Speed was not, perhaps, the root of all evil, but it was the symbol of a number of other even graver ills which beset us. This modern age of speed was also the age of chronic fear. We feared silence and surrendered ourselves to the tyranny of meaningless noise. We feared contemplative thought and enmeshed ourselves in feverish activity. We feared solitude and became puppets in a crowd. It had been proved that noise reduced efficiency and slowed down the rate of work. How many people devoted an hour a day to contemplation, or 10 minutes to constructive thought? Many people gave themselves no time for abstract thinking, with the result that the great literature of yesterday was unread and the great literature of to-morrow unwritten.

Controlled Speed

Air Vice-Marshal J. M. KILPATRICK devoted his speech, opposing the proposition, to experience in aviation. To-day we contemplated with no particular sense of awe or of the unusual the fact that aircraft could be flown at the speed of sound or beyond. This was an age of speed, but also an age of speed control. The speed of piloted aircraft had risen tremendously in the last 30 years. In 1918 their cruising speed was 100–120 miles an hour; to-day, with the coming of the jet engine, it was 400 miles an hour. It was required of men who flew aircraft that they must be fit, but the physiological standards demanded of the crews had not increased with the increase of speed. Uniform speed of itself presented no particular hazard. There were, of course, hazards in altitude flying—chiefly anoxia—and high altitudes were ventured in attaining speed, but the provision of oxygen in the aircraft or of pressurized cabins enabled a young healthy man to fly competently at very considerable heights. The question of acceleration came in; rapid changes of vertical acceleration from positive or negative might lead to motion sickness, but this was not particularly a hazard belonging to the age of speed. The visual blackout which came on turning at high speeds, due to centrifugal force and consequent fall in blood pressure in the central artery of the retina, could be postponed by special devices. He added a few words about the psychological problems of high speed flying. Close attention and swift reaction were demanded in certain conditions, but this was met by training a man so that he was able to deal with the situations which arose, and instrument presentation was so arranged that the pilot could be "fed" with information in a simple form. Aircraft were flown successfully at very high speeds and under perfect control, and surely this was a strong reason why the proposition before the meeting, that speed had outrun human adaptation, could not be accepted.

Mass-produced Man

The BISHOP OF PONTEFRACT (Rt. Rev. A. H. Morris) brought the audience back to earth by asking whether any doctor could deny that the number of cases of nervous breakdown had increased tremendously. We were being rushed off our feet from the date of our birth until our departure for what he hoped was a more peaceful existence. He instanced the school curriculum, and suggested that pupils were being rushed through their education. In the Health Service the shortage of doctors and nurses was making too large demands upon those who were engaged in it, and the same was true, in their field, of the clergy. Mechanical transport had had the effect of increasing the speed at which they all had to work. The result was that men themselves had become mass-produced and there was no time for leisure or the cultivation of the mind. Could anyone say that human adaptation had kept pace with man's destructive tendency?

The fourth of the announced speakers, Mr. RAYMOND MAYS, spoke as one whose interest was motor-racing, and contested the proposition on much the same grounds as the air vice-marshal. His complaint was not against the increasing speed of cars—far from it—but against the static road, which had not kept pace in this evolution. He considered it a great mistake to think that machines should be brought down to suit the individual; it should be the other way about.

In the course of some brief general discussion Lord SEMPILL drew the attention of the audience to the fact that James I (James VI of Scotland), whose portrait was hanging in the Apothecaries Hall, and who belonged to an age of slow motion, wrote a long treatise on peptic ulcer, not to speak of his *Counterblaste to Tobacco*.

On a show of hands the meeting declared itself, by 59 votes to 57, against the proposition that the age of speed has outrun human adaptation.

Reports of Societies

MEDICATION IN GENERAL PRACTICE

A discussion was held on November 21 by the General Practice Section of the Royal Society of Medicine at 1, Wimpole Street, W.C.1, on "Medication in General Practice."

Dr. R. J. F. H. PINSENT opened the discussion with an account of an experiment that he had carried out in a busy industrial practice during 1950. During that year he had had 7,064 consultations with patients: 1,458 required only his signature or some other administrative act, leaving 5,606 to whom treatment was given; this was recorded and formed the basis of a classification into which the consultations were arranged as follows. In *Category A* (10–15% of consultations) a specific treatment was given. This type had a varying seasonal incidence and occurred most frequently in winter and spring, since the treatments included antibiotics and immunization; other specific therapy, however, such as insulin, liver extract, and iron, was given regularly throughout the year. In *Category B* (about 10% of consultations) symptomatic treatment was given with drugs designed to alleviate symptoms as well as to affect the course of the underlying disease. These consultations were constant throughout the year and the drugs given included adrenaline for asthma and barbiturates as suppressives in epilepsy. *Category C* (20–25% of consultations) also comprised those having symptomatic treatment, but there the treatment was

regarded as being more suggestive than pharmacological. Stock mixtures, ointments, and lotions, for instance, were more useful for the suggestion that accompanied them than for any alleviation of symptoms they directly produced.

Health Education versus Placebo

In *Category D* (less than 10% of consultations) a placebo was given. It was important that that treatment should be recognized in the mind of the prescriber as being without any action other than suggestion. In prescribing placebos deliberate use was being made of faith in the minds of many older patients that the doctor knew the remedy uniquely applicable to their cases. Patients under the age of 40 were not given placebos, receiving instead advice and guidance on how they might help themselves to overcome their own problems. Medication was replaced by a conscious effort at instruction of the patient. In *Category E* (40–50% of consultations) the patients received no medication at all. They were treated purely by advice and health education, their symptoms explained and worries put at rest. The young man who feared tuberculosis was given the therapy of a full clinical examination, the woman having her first baby was told what to expect, and the elderly patient was taught how to live within but not beyond his failing strength. Replacement of medication by advice was well accepted by the patients, though some whose confidence could not be retained were no doubt lost to the practice. The numbers so lost were not such as to affect the size of the practice, which was deliberately limited in order to permit the performance of a reasonable standard of work. Dr. Pinsent ended by saying that he felt that this way of dealing with patients, by giving them advice rather than medicine, could be considered a return to the classical conception of a doctor as an adviser and a teacher to his patients, showing them how to stay healthy as well as attempting to cure them when they became ill.

Diagnosis before Treatment

Dr. J. MALINS, who described himself as a general physician with a great interest in the problems of general practice, said that he would like to put forward the view that any such classification by treatment should be based on a complete diagnosis. It was an abuse of vitamin B_1 to use it for all forms of neuritis, or of iron for hypochromic anaemia when no account had been taken of the underlying menorrhagia or bleeding piles, or of liver for undiagnosed and unestablished pernicious anaemia. On the other hand, a diagnosis could in many instances be made by the use of drugs: in pneumonia there was no point in searching for cold agglutinins before it had been found whether the disease was drug-sensitive or not, but this principle could only be used where the action of the drug was certain; no successful diagnosis of disseminated sclerosis could be made by treating the patient with liquor arsenicalis. Many irrational views on treatment were held by general practitioners, and these were often perpetuated and intensified by drug firms. For instance, he questioned the advantage of digitalis glycosides over the preparations of the cheaper and more familiar digitalis leaf; the value of opium in controlling pain and discomfort in cases of advanced malignant disease was certain, but many expensive analgesics were used which had little advantage where toxicity and addiction were of no great significance.

More Treatment in the Home

Many modern drugs needed laboratory control, and he thought that it was important that this type of control should be made easily available to the general practitioner. He would also like to see an extension of the district nursing service to include a service for giving injections or even blood transfusions to patients in their own homes. He was convinced that the Government could save money on the hospital services by spending more on the general practitioner service, thus saving patients who could easily be treated in their own homes from ever going into hospital.

He endorsed Dr. Pinsent's view that a doctor's function was to give advice rather than nostrums to his patients. To do this well he needed a wide education in the humanities rather than in the intricate technicalities to which medical students were subjected.

More Views on Placebos

The subsequent discussion was mostly concerned with the use of the placebo, nearly all speakers commenting on its value. Dr. G. O. BARBER said that he used a placebo for patients with a mild anxiety neurosis, as he believed that a bottle of medicine to be taken at certain intervals was a useful peg on which to hang a regime of treatment. When night came fears and anxieties were liable to return, and the bottle of medicine was a tangible reminder of the doctor's presence and of his advice. Another speaker disagreed with this; he believed that a placebo could in many instances perpetuate or even create an obsession. Patients who showed signs of neurosis should not be given medicines unless medication was likely to do them positive good. Dr. L. W. BATTEN always gave a sedative where a placebo seemed necessary. Dr. M. C. ANDREWS thought the use of a placebo was often the only way a doctor could save himself from argument with an unintelligent patient; that it could also be of real value was shown by the difference the patient's attitude of mind could have on the pharmacological action of really active drugs such as morphine, whose effects were totally different on the patient told to keep hard at his work and the patient lying in bed. Several speakers emphasized the importance of colour in placebos, but Dr. G. F. ABERCROMBIE thought that perhaps it was pressing the point too far to use pink medicine for girls and black for strong men, and Dr. DELISLE GRAY told of a patient given a bottle of colourless liquor arsenicalis who, thinking that the colour was a measure of the potency, drank it at a draught and developed symptoms of acute arsenic poisoning. Dr. G. M. KERR thought that general practitioners should see that the cure was not worse than the disease. They must sometimes control consultants, making certain that the effectiveness of treatment justified any excessive unpleasantness or side-effects.

Many speakers commented on the large proportion of patients whom Dr. Pinsent had treated with argument and health education rather than with medicine. Dr. Kerr thought that this depended greatly on the personalities of doctor and patient, and that in the hands of some practitioners the bottle of medicine was more appropriate. Others felt that Dr. Pinsent's approach was an ideal state of affairs, their chief reasons for not doing the same in their own practices being that it was quicker to give a pill than advice, and that patients tended to desert a practice where the traditional bottle of medicine was not given.

Copies of various filmstrips likely to prove useful in the ordinary teaching of medical students and nurses can be obtained from Dr. Brian Stanford, 54, Upper Montagu Street, London, W.1. *Lumbar Puncture*, originally made by Manchester Royal Infirmary for teaching nurses, has 24 frames in a sequence which illustrates by photographs and diagrams the site of operation, how it is found in recumbent and sitting patients, and every phase of the technique. This is so well done that each picture makes a deep impact on the viewer and the main points are henceforth remembered without effort. A booklet provides the lecturer with information about each picture, and this also is well prepared. The price (10s.) seems very reasonable. *Breast-feeding* is the title of three filmstrips made for the Department of Child Health at Guy's Hospital: anatomy, physiology, and diseases of the breast; antenatal and postnatal care; and the achievement of successful breast-feeding. Again the visual presentation is extremely clear and memorable, and much to be preferred to somewhat haphazard blackboard diagrams, odd charts, and the like so often employed in medical teaching.

Correspondence

Invite Russian Doctors

SIR,—I should like to propose that the B.M.A. should carry out an experiment in peace-making. When I say an experiment I mean a scientific experiment, very carefully planned and on a substantial scale. My suggestion is that we should communicate with the Russian Government through our Foreign Office and invite the Russian medical profession to send a party of doctors to London as the guests of the B.M.A. It would be made clear that the invitation would *not* be to discuss politics or attend conferences; they would be asked to say what they would like to do or see.

I suggest that an experiment on these lines should be discussed in your correspondence columns and that if it is approved a subscription list should be opened. If a big enough fund is subscribed a committee should be appointed to set the experiment going. If the Russians responded the B.M.A. could then expand it. For example, the Law Society might be asked if they would invite their opposite numbers, and other associations would send invitations. The next step would be for the trade unions to join in on a national scale.—I am, etc.,

Wetherby, Yorkshire. R. L. KITCHING.

Post-leucotomy Anxiety

SIR,—I recently met a patient who had had a prefrontal leucotomy after several years of treatment, and he was again becoming worried, unhappy, and discouraged. The leucotomist had been extremely satisfied with the result, and so had the patient, having much awareness of his previous condition and feeling now capable of resuming his previous occupation. His difficulty was that no firm would give him a post of any responsibility owing to his history of leucotomy—nor would or could the leucotomist do anything to remove the diagnostic label with its implications, beyond urging him to resume a normal life. His fiancée was still willing to marry him, and able at a pinch to support him. His lay psychotherapist strongly urged him to get married on these terms and lead a normal life, but the patient strongly resisted the idea that a man can marry with no prospect of ever being able to support his wife—and was very discouraged at the seeming impossibility of making a new start.

I told him very definitely that his worries were normal, right, and proper to his circumstances; that his leucotomy had been even more accurately done than the leucotomist could have dared to hope, since he had lost all his previous turmoil, but none of his capacity to reason and understand, to feel and act on moral values; that he was, in short, a 100% normal man in very difficult circumstances. I advised him to give up all idea of his previous business, at which he would have been a success if entry had been practicable—and borrow from his father the capital to buy a small one-man shop. This he has done and married on his prospects.

Leucotomy was right, necessary, but insufficient. Something more was needed, possibly in the field of psychoanalysis or some other school, perhaps only common sense. Finally it was necessary to find the moral courage dogmatically to remove the diagnostic label and pronounce the state of cure.—I am, etc.,

Crowthorne, Berks. H. D. FORBES FRASER.

Traumatic Rupture of Aorta

SIR,—In the article by Dr. Donald Teare (September 22, p. 707) the opinion was expressed that the mechanism causing rupture of the thoracic aorta in air-crash victims was acute flexion of the body over a safety-belt.

I have observed traumatic rupture of the descending thoracic aorta in four persons during the past three years and my concept of its cause is quite different from that expressed by Dr. Teare. Three of these cases resulted from three different automobile accidents, and one case resulted from a fall from a roof in which the person landed on his feet. In all cases the rupture occurred immediately distal to the arch of the aorta at about the level of the attachment of the ligamentum arteriosum. In three of the four cases the tear extended completely around the aorta with separation of the torn ends. In two of the cases, including the one resulting from a fall, the ruptured aorta occurred as a single lesion, with no evidence of any crushing or flexing injury of the chest or spinal column. Indirect rather than direct trauma must be considered causative under such circumstances as these, and my concept of the causative mechanism is a sudden swaying downward of the abdominal viscera and diaphragm with a consequent pulling downward of the aorta which is anchored to the viscera and diaphragm. The aorta is anchored upward most firmly at the arch, both by the dense connective tissue in this region and by the large branches running upward from the arch. The tear or rupture, as a consequence of this, occurs quite constantly immediately distal to the arch. The occurrence of this mechanism in automobile accidents is explainable by assuming that the victim was in a semi-reclining or supine position at the time when the vehicle came to a sudden stop.

Dr. H. K. Fidler came to a similar conclusion concerning the causative mechanism of traumatic rupture of the aorta in a study of eight cases collected over a six-year period, and including one air-crash victim (*Canad. med. Ass. J.*, 1949, **60**, 590).—I am, etc.,

New Westminster, British Columbia. P. S. RUTHERFORD.

Counting Eosinophils

SIR,—I am sorry to refer to statistical methods, just at a time when letters are appearing in the *British Medical Journal* decrying their use. However, an article by Dr. J. C. W. MacFarlane and Mr. G. W. Cecil appeared in the *Journal* of November 17 (p. 1187), to the results of which a statistical analysis might well have been applied. A table showing the results of 30 series of eosinophil counts on 10 cases is given. The purpose of this table is to show that the second series of counts performed on each case shows more variation than the first and third series, due to clumping of cells. The table undoubtedly does show this. However, a statistical analysis of the first and third series of counts from each case reveals that there is far less variation in these series than is likely to be achieved in any system of random sampling.

It is not possible to mix cells suspended in a pipette so evenly that every counting chamber filled from it will contain the same number of cells, or anything like the same number, particularly when that number is small. There will always be a chance variation equal to the square root of the mean and the counts will be distributed in a Poisson series. Assuming that the technique was perfect the chance that the result shown would occur is less than 1 in 100. A statistical analysis thus reveals what is not immediately obvious from the results of this research work—namely, that the results are too even to have arisen by chance, and imply some error in the technique of counting. No conclusions can be drawn from these results, therefore, about the quality of either the modified or unmodified diluents.—I am, etc.,

Sunderland. T. MANNERS.

Educating the Public About Cancer

SIR,—There are statements in Dr. James F. Brailsford's letter (November 10, p. 1154) which must be answered. As one who in the last 50 years has seen a continual improvement in the results of the treatment of malignant growths by *x* rays, radium, and surgery, I cannot but be astounded by the pessimistic attitude expressed in this letter and the implied suggestion that these methods have very little value.

I still have, to my certain knowledge, two patients alive and free from any obvious return of the disease over 40 and over 39 years after treatment, the one by *x* rays and

the other by radium, and both were proved by section. Another case died two years ago, 40 years after treatment by radium, and it must be remembered that these cases were treated in the very early days of radiotherapy. To the general public these cases count as cures. Perhaps Dr. Brailsford attaches a different meaning to the word. Among medical men we prefer to talk of 5-year, 10-year, 40-year, and so on survivals, but to the public they are cures. Will not Dr. Brailsford even admit that a case of an inoperable carcinoma of the rectum, treated by a combination of radium therapy, surgery, and again radium therapy, living free from growth for 23 years and dying of old age when nearly 90, as a cure?

The citation of Mr. Furnivall's letter is unfortunate, as radiotherapists immediately assumed that he was dying of malignant disease and that the patient was being told the usual tale about the wicked radium. As this seems to have a better psychological effect on the patient one has to permit the slander, but it may do harm to radium or *x*-ray treatment if it is spread about.

Some few patients who have survived for many years may die of a malignant growth, sometimes of a different nature and sometimes indeterminate. This is quite understandable if one realizes that cancer or malignant growth is not a disease but a process in the same way that inflammation is a process, and both have several different causes. In the case of malignant growths evidence is very strong that two separate factors must come together to start the process, but, once started, removal of one or perhaps even of both the causes will have no effect in staying the process.

In my time I have seen continual improvement in the results of treatment in these conditions for various reasons: the earlier treatment of the process and the prevention of some of the causes; clearer understanding of the lines of spread of the different types and which cases are suitable for treatment and what is the best method to use; improvement in radiotherapeutic and surgical techniques and the availability of better types of radiation and of better aids to surgery; a much better attitude of most surgeons in working with the radiotherapists instead of against them.

In the education of the public, the question is, Does the good done in getting earlier cases more than counterbalance the harm done in causing cancerphobia? I am one of those that believe it does.—I am, etc.,

Cobham, Surrey. N. S. FINZI.

Early Diagnosis of Cancer

SIR,—With the advance in surgical and anaesthetic technique which has taken place in the last two decades, the early diagnosis of malignant conditions assumes more than academic importance. General practitioners are constantly being exhorted to be on the alert for possibly malignant lesions, so that early cancers can be submitted to radical surgery.

In the past two years I have had three cases which could probably have been diagnosed at an earlier stage. In the first two of these surgery might well have proved life-saving. The third case illustrates a somewhat different point.

The first case was an unmarried woman aged 49, previously in perfect health, whose only complaint was dyspnoea. Examination disclosed expiratory difficulty with numerous rhonchi scattered throughout the whole right lung. There were no signs on the left side. The suggestion was of partial obstruction of the right main bronchus. She was referred to a hospital physician, who agreed, from his clinical findings, with that conclusion and submitted her to radiography. The lung fields were clear, and, despite the clinical evidence, the patient was dismissed by the physician. Six weeks later the patient developed a massive pleural effusion which was shown subsequently to be due to bronchial carcinoma. In view of the physical signs, was not bronchoscopy indicated?

The second case was a married woman, aged 29, who had a small haemoptysis and whose general condition was poor. She was referred to the tuberculosis dispensary. There she had a series of chest *x*-ray photographs which were indefinite but not suggestive of tubercle. Meanwhile her general condition continued to deteriorate and she began to develop considerable pain. About two months after the initial consultation she was found to have a large bronchial carcinoma. In view of the obscurity surrounding the original investigation, was not bronchoscopy indicated?

The third case was a married woman of 67, until then in good health, whose complaint was intestinal colic. This was not relieved, indeed it progressively increased in severity, during medicinal treatment with full doses of tr. hyoscyamus and a liquid paraffin preparation. She was therefore sent to an out-patient department with a request for radiological investigation. Her daughter, who accompanied her, was informed at the hospital that *x*-ray was unnecessary. The surgeon informed me that her symptoms were due to constipation. It was then decided to consult a surgeon privately, and a barium enema arranged by him disclosed carcinoma of the colon. On laparotomy there were multiple metastatic deposits throughout the peritoneal cavity.

With regard to the last case I have described, it is my belief that sometimes failure in early diagnosis results from the practice of a false economy at the out-patient department. No doubt this is partly imposed by the limitation of hospital expenditure ordered by the Ministry of Health. The other important factor is the serious shortage of *x*-ray film obtaining in Britain at the present time. I am told that the reason for this is that the films are being exported to earn dollars to help solve the balance-of-payments problem. If this is so, then I say it is a national scandal against which the medical profession and the *British Medical Journal* should be crying out. There are many things more precious than dollars—and one of them is life.—I am, etc.,

Glasgow. R. LESTER BLACK.

Our Daily Bread

SIR,—Dr. J. B. M. Coppock and Mr. S. Walter Butterworth (November 3, p. 1091), criticizing Sir Edward Mellanby's paper, state bread is bought by weight and so it does not matter how blown up with air is the loaf. But the average family only eats as many slices of bread as can be covered by the ration of butter, margarine, jam, etc. Therefore, if the slices weigh less, less nourishment in the form of bread is taken: this is what Sir Edward said.

Of real value would be an explanation from your two correspondents of why English flour after such elaborate treatment still makes such poor bread compared with French flour, which is not treated—why, indeed, English bread, according to travellers, is the worst wheaten bread in all the world. English bread has ceased being a food in its own right and is now only regarded as a tasteless vehicle for other foods. No one eats it for itself alone. Yet untreated 81% extraction stone-ground flour makes bread which is in itself so pleasant, so definitely a real food, that it can, even when stale, be eaten alone. Somehow the British Baking Industries Research Association have adopted a wrong policy: while trying to make a foolproof uniform flour for baking they have succeeded in producing a curiously dead loaf which no one would eat were any other food available. I fear that whether or no the association is poisoning our bread with agene, etc., it is certainly making us regard bread with a contempt never before accorded to it in the whole history of man.—I am, etc.,

London, W.1. FRANKLIN BICKNELL.

SIR,—Dr. Franklin Bicknell's letter provides a further instance of the inaccurate statements that are made from a lack of appreciation and knowledge of the factors involved in bread-making.

1. As pointed out previously (November 3, p. 1091), there is a finite limit to the amount of air a loaf can contain, and the ultimate effect of flour improvers is simply to lengthen the slice somewhat, as the girth of the loaf remains unaltered due to the restriction imposed by the tin in which it is baked. As the weight of bread in the tin is constant and regulated by law each slice of bread of given thickness will continue to weigh the same irrespective of the flour or dough treatment and provide almost exactly the same amount of nutrients. Flour and bread consumption figures also suggest that changes in the available quantities of butter, margarine, and jam largely manifest themselves in more or less generous distribution on the slice depending on the trend in the supply.

2. French bread is essentially different in size, shape, composition, and crumb texture from the tin or batch loaf widely consumed in Great Britain. Such breads are not comparable nor are they related to the type of flour used in their preparation, but to different methods of production and fermentation to meet differing national tastes. French batons or French sticks can be prepared from British flour of suitable strength and would yield these varieties in equal quality.

3. The reference to stone-ground flour is not clear, inasmuch as this type of flour usually approaches 100% extraction. 81% extraction stone-ground flour can be prepared and would, of course, contain substantially the same nutrients as national flour. It is well known, however, that bread prepared from high extraction flour (excluding processed germ flour) stales more rapidly and is more prone to become mouldy than bread prepared from flours of low extraction.

4. The British Baking Industries Research Association is in no way responsible for the variable flour grists, nor since it was formed five years ago has it tried to make a fool-proof uniform flour, nor does it carry out agene treatment, regarding which, as recently as November 12, Dr. Bicknell should know that the Minister of Food stated there is no evidence that the use of this improver is harmful to human health. The association's sole concern is scientific research into all aspects of baking, including the production of good bread. It is, however, interested in what the consumer prefers and an advocate of freedom of choice in this matter.

—I am, etc.,

Baking Industries Research Association, Chorleywood, Herts. JOHN B. M. COPPOCK.

SIR,—Dr. Bicknell interprets Sir Edward Mellanby's statements about bread volume and weight, but I am unable to accept his version. Bread is bought by weight and is eaten, not by slice size, but by appetite. Appetite is affected by many factors, and so is the demand for bread, which fluctuates considerably throughout the year. These fluctuations, however, are in no way related either to the rations of butter or margarine or to the consumption of unrationed spreads such as jam. In his concluding paragraph Dr. Bicknell compares the merits of French and British bread. I think that his assertions are untrue, hence the necessity for explanation does not arise. Good bread is made in France and in this country, but tastes differ. The French have a phrase for it—"Chacun à son goût."—I am, etc.,

Bramhall, Cheshire. S. WALTER BUTTERWORTH.

The Doctor and the Courts

SIR,—In June I was asked by the police to examine a patient of mine, who was 15 years old, about seven and a half months pregnant, and they were proceeding against a man on the grounds of carnal knowledge. On August 10 she gave birth to a boy, and the case had to be postponed until September 25 and was heard before the local magistrates. My evidence, which was uncontested, consisted in giving my name and address, agreeing I was a registered medical practitioner, and confirming that I had examined her on June 18, and confined her of a full-term child on August 10. I was then warned for the assizes at Lincoln (37 miles away) in October, and duly attended on Wednesday, October 31, and Thursday, November 1. My evidence was precisely as before, was unquestioned by counsel for the defence, I was released from the court, and allowed to go home. I was in the witness-box, at the maximum, five minutes.

Those are the bare facts. An uncomplicated case of carnal knowledge, uncontested by the man on the grounds that he thought she was older. At no time was my evidence questioned, since her pregnancy had not been queried and the paternity did not enter into the case. Yet I had no option but to accept my recognizance, although I could not see how I could add anything to what I had already sworn. The subsequent events, to which I take marked exception, are the grounds of my complaint. From September 25 until the late evening of October 30 I could never get any definite statement whether I should be wanted, and my appeals for some prior knowledge, so that I could make arrangements for the running of my practice while I was away, were useless. On October 30 I was told to be at the assizes at 1.45 p.m. on the 31st. I was there at the time requested, told my case would be on just after 2 p.m., and at 4.45 p.m. was told to go home and be at court again on November 1 at 10.30 a.m. Again, I arrived at the time requested, waited until I was called at 4.40 p.m., gave exactly the same evidence I gave in the magistrates' court on September 25, was not questioned, and was out of the court by 4.50 p.m. I had travelled 148 miles, missed three surgeries and one and a half days' visiting, been at the court just over nine hours, to give evidence for five minutes.

All over the country at magistrates' courts, sessions, and assizes, the same procedure is going on with the same fantastic waste of time and the same complete indifference to doctors' responsibilities and commitments. Any complaints are ignored or evoke some platitude like the "Majesty of the Law." I am querying exactly what is the "Majesty of the Law" which is advanced as an excuse, and who comprises it. Who decides in what order cases shall be heard, why are there such delays, and who is responsible? Why must we submit to the almost contemptuous manner in which we are bluntly told to go home and come the next day, and even the day after that, if necessary, without any inquiry whether it is convenient? Who bears the responsibility if anything happens in our absence, because, not knowing how long we should be at the court, we have not been able to make arrangements to cover everything? What excuses could we advance, with what success, should we have to appear before the executive council to answer the charge of an irate patient that we had not fulfilled our contract and been absent from our surgeries? Finally, why have we become so unimportant that these conditions have continued so long without complaint? Why do we meekly accept this state of affairs that allows us to be penalized for any petty breach of our contract at the hands of a patient, yet tolerates our being kept hours or days attending courts with indifference to what is happening to our practices or what personal hardship we may be suffering in our homes?

It is time this matter was discussed, because I am not satisfied there is no way to alter it. We no longer live in the far-off days of calm leisurely practice, and we have not all got assistants or partners. I am lucky in that I have three colleagues, technically my opposition, whose relationship with me in practice makes them almost partners and is remarkable in an era of increasing competition. Consider the country practitioner, with a solo practice and no colleague near enough to do his surgeries and rounds in his absence although he might do an emergency. Who would do the emergency confinement or street accident or field accident if the stand-by could not be found? Who would attend the acute abdomen? It might be said that even if the absent doctor was at home he might not be found in time. He would be found quicker in the environs of his own practice, and be able to do something, than if he had been, like me last week, stuck for nine hours at Lincoln Assizes, 37 miles away.—I am, etc.,

Bourne, Lincolnshire. GEORGE HOLLOWAY.

Secrecy of Psychiatric Case Records

SIR,—I read Dr. Ellis Stungo's letter (October 13, p. 913) with special interest. The dangers of breach of confidence to which he refers are real and they are not confined to psychiatric clinics. I am not sure that I agree that his suggested solution to the problem is the most efficient one. It is quite possible that at the cost of yet another register or card index and yet another series of numbers (in addition to the normal hospital unit number and master index) the anonymity of the patient could be preserved. This, however, would not prevent staff from bandying intimate (though anonymous) details if they wanted to gossip. The only effective cure is to stop gossip. It may be "too much to

expect young people to overcome their curiosity" but it is not too much to expect them to understand that in handling notes made by clinicians they are included in bond of confidence between doctor and patient (and that legal penalties may be involved—e.g., in libel actions). They may keep their eyes open but they should keep their mouths shut.

It is because the necessity for this discipline is recognized that the creation of distinct Records Departments has been urged and developed so that records, and staff handling records, can be under the effective control of a trained officer with a sense of the trust placed in him (or her). This officer if properly trained should not only ensure the maintenance of good records with maximum accessibility to clinical staff but also should ensure *inaccessibility* to unauthorized persons, or persons not adequately disciplined (by his supervision) to respect confidential matters. Most records officers not only impress on new employees entering their department the need for this respect, and the reasons for it, but inflict severe penalties for any lack of discretion they observe. They feel it is better to establish a code of professional conduct in medical records custodianship with resultant increased pride and enthusiasm in staff than to put up fences which have bad psychological effects and are of doubtful efficacy. Staff react well to being trusted; in the rare cases where they do not, action can be taken.

Dr. Stungo says, "It is not too much to expect hospital authorities to take steps to prevent such breaches of confidence." By and large, through the records officer, where he exists, hospitals are safeguarding secrecy very efficiently. —I am, etc.,

Association of Medical Records Officers. B. BENJAMIN, Chairman.

Laryngeal Epilepsy

SIR,—The letter of Dr. W. Raymond Parkes (September 15, p. 672) raises points of real interest. In April, 1936, I published in your *Journal* an article on laryngeal vertigo with a description of a case and a detailed account of all the publications I could trace since-Charcot's original contribution, which was dated November, 1876. In the same year (1936) Dr. Hugh Barber published an almost identical case (*Guy's Hosp. Rep.*, 86, 350) and gave a clear and valuable analysis of the syndrome. In June, 1936, I published three further cases (*Glasg. med. J.*, 125, 278). At a subsequent meeting of the Association of Physicians of Great Britain and Ireland Dr. Hugh Barber and I initiated a discussion on this syndrome, and it became obvious that the present generation of clinicians does not appear to be familiar with the condition. From the discussion at this meeting many members of the Association stated that they realized that they had seen cases from time to time in bygone years, but had not recognized their exact nature or classified them in the groups described by Charcot.

In my original article I stated that from an analysis of cases I had personally examined, and from a review of all the literature, it appeared to me that attacks of this nature fall into one of three groups. In the first group one would place the cases in which coma follows severe and prolonged coughing, accompanied by respiratory distress and dyspnoea. In the second group might be included cases with a laryngeal aura followed by coma and clonic movements. The manifestations occurring in this group of cases would presumably justify the diagnosis of laryngeal epilepsy, which could not reasonably be applied to the other groups. In the third group one would place cases where a slight attack of coughing preceded by a tickling sensation in the larynx is followed by momentary coma without clonic movement of any kind.

The cases I have personally seen and studied fall into group three and have one common factor—irritation of the larynx. The resulting attack of coma would suggest that such patients are in some way, which we do not understand, susceptible. I also suggested that the involuntary inhalation of a few drops of cold water into the larynx of susceptible persons while swimming might result in drowning. In most of such cases the coroner's inquest returns a verdict of cramp, of which there is no proof.

It does not seem to me reasonable to classify these three groups, with such essential points of clinical difference, under the same title, whether it be laryngeal vertigo or laryngeal epilepsy. On the facts available the exciting cause in these three types of cases must be different. If this line of thought is correct we are clearly dealing with three distinctly separate diseases, which should be so regarded.

My reason for raising the matter again is to draw attention to the very considerable degree of medico-legal importance in cases of this nature. It is a common occurrence for medical witnesses in courts of law to be ridiculed and discredited when they describe an illness accompanied by partial or complete loss of consciousness as a defence of patients charged with serious accidents resulting from such an involuntary attack. In 1928, in conjunction with Sir David Henderson, I gave evidence in the High Court at Stirling in the case of *Rex* v. *Ritchie*. Sir David Henderson and I were convinced that the patient, when arrested on the charge of homicide, was suffering from partial mental dissociation due to toxic and exhaustive factors. Lord Murray and the jury agreed with this view, and the late Lord Moncrieff told me in a personal conversation that this case was of great legal importance. The fact remains, however, that this defence was regarded with scepticism amounting to hostility in high legal circles, and so far as I can ascertain this attitude still persists.

There is a recent tendency for the lay press, legal authorities, and medical journals to use the phrase "black-out." I have never personally understood quite clearly what this phrase means, as it may be attributed to so many conditions. This at least is certain: the phrase is inaccurate and unscientific. I therefore think it should be avoided by our profession. An illness which is accompanied by sudden and complete loss of consciousness is of great importance, especially in motoring, flying, and swimming. Medical knowledge and medical practice have always been based on trial and experiment, accurate observation, and the search for truth. Legal practice, so far as I can ascertain, is largely governed by precedent. Were the medical profession similarly shackled scientific advance would be quite impossible. I therefore feel that the points raised by Dr. Raymond Parkes are of great importance, and I certainly hope that his letter will produce further communications based on recent personal experience. It is almost certain that this disease is most often seen by general practitioners, and it will be extremely interesting to learn if any one of our profession has actually been an eye-witness of a seizure of the type originally described by Charcot.

Members of the medical profession cannot be expected to alter or modify medical facts to suit legal theories, but I do feel a real endeavour is necessary to place seizures of this type in a well-defined category which will receive medical recognition and support. In even the most recent textbooks laryngeal vertigo is omitted. Its inclusion in standard works might perhaps help towards its recognition by the legal profession, who can hardly be expected to accept as reliable evidence rare monographs written last century in a foreign language.—I am, etc.,

Glasgow. DOUGLAS K. ADAMS.

Toxic Effect of Proguanil

SIR,—The letter from Dr. Peter Abbott (August 18, p. 419) prompts me to endorse his views on lack of long-term toxicity of proguanil. In 13 months' experience with this drug in malaria prophylaxis in Manus Island in the South Pacific no white patient reported sick with symptoms relating to prolonged exhibition of proguanil. A few persons found that it made them sleepless when first taking it, and if the insomnia persisted they were advised to change to other antimalarial drugs. However, as all these cases of so-called intolerance to proguanil occurred early in the sojourn of the patients on the island, factors of sudden climatic change (it takes only two days to reach Manus from Sydney by air) and the necessity of mental readjustment to a different mode of life together with a change in diet cannot be entirely excluded as contributory causes of the sleeplessness.

Until recently Manus malaria (mainly of the benign tertian variety) was completely suppressed by a daily dose of one proguanil tablet. However, either the present Manus strains

are becoming resistant to proguanil or else an already proguanil-resistant strain has been introduced to Manus from the mainland of New Guinea, for several patients were seen towards the end of my stay there who contracted slide-positive benign tertian malaria despite (their veracity was not in question) the above-mentioned suppressive routine. The administration's solution to this problem is the advocacy of a double daily suppressive dose. The question may well be asked, When will this process end? Presumably, when a strain similar to that reported in *Nature* (1951, **168**, 332) is encountered, we shall have to take 55 tablets of proguanil daily.—I am, etc.,

West Ryde, N.S.W., Australia. ROLAND G. CHAMBERS.

Disappearing Naevi

SIR,—In his interesting communication Dr. F. Parkes Weber (October 27, p. 992) refers to the spontaneous disappearance, or partial disappearance, of certain types of naevi in children. The incidence of naevi in the newborn, particularly on the forehead, in relation to the eyelids, the root of the nose, and the nape of the neck is much higher than many realize. Most of these disappear during the first year of life. The fact is not so widely known that in women there is a tendency for naevi to appear and sometimes to grow rapidly during pregnancy, only to regress equally rapidly in the puerperium. This tendency is particularly marked with naevi of the face, lips, tongue, and gums. Their growth is sometimes so rapid during the later weeks of pregnancy that they are mistaken for malignant tumours. It is interesting that the sites in which they are found so closely resemble those in which naevi of the newborn commonly occur. It would seem reasonable to suggest that the same maternal factors (probably hormonal) are responsible for these similar manifestations in both mother and infant.—I am, etc.,

Oxford. JOHN STALLWORTHY.

Treatment of Migraine

SIR,—The excellent annotation on this subject (September 1, p. 538) has been followed by correspondence (September 15, p. 673), and as one who suffered severely from migraine from boyhood until the late fifties I think my personal experience will be of interest.

My attacks came on quite suddenly and occurred from once to several times a week, interfering with schooling during specially bad weeks. The worst attacks occurred during the 1914–18 war, and on one occasion the attack was so severe that it became necessary to hold on to a railing with my right hand while my left arm and leg were in constant tremor. During that particular attack my mind was so confused that I could not have given my name. It was followed by a dazed feeling in my head for some hours before finally passing off. In one instance just before entering the examination hall for the paper on medicine I experienced so severe an attack that vision became difficult and I could not read one word of the paper for nearly an hour.

The actual attack always presented in the same sequence: an ache suddenly occurred in the right supraorbital nerve immediately above the eye, and was quickly followed by a feeling of tightness just inside the skull about an inch higher up than the ache. It always seemed to me to be a constriction of an artery. Soon afterwards there was marked throbbing slightly to the outer side of the apparent constriction, and while the throbbing lasted the headache continued, and the worse the throbbing the more intense the headache. The duration was usually for some hours only, but in bad attacks it lasted for 24 hours or more.

Although during the attacks I experienced some nausea I never vomited. Usually a neuralgic pain over the right forehead followed the attack and gradually disappeared. The sight of the right eye always became blurred until the migraine passed away. My eyesight had been fully corrected since my youth.

Various drugs were tried for relief of the pain, but usually without much, if any, success. I found the most useful to be tablets of phenacetin, caffeine, and aspirin. Much more relief was obtained by cold-sponging the right temple and the top of the head. No cause for the migraine was discovered.

Fifteen years ago I was treated successfully for an affection of the right antrum and ethmoid, sphenoid, and frontal sinuses, and there is no doubt whatever that since that time I have hardly ever been troubled with migraine. This may be important in other cases, but probably there is more than one affection capable of causing arterial spasm.

I might mention that as a child, and until the age of 20, I suffered from white (dead) fingers in cold weather, evidently owing to spasm of the artery, and a brother of mine who also suffered from migraine was similarly affected.

—I am, etc.,

London, N.W.8. BERNARD MYERS.

Acute Tuberculous Septicaemia with Leucopenia

SIR,—The cases described by Drs. K. Ball, H. Joules, and W. Pagel (October 13, p. 869) prompt us to publish the following case.

A business man, aged 62, was admitted on August 1. He complained of vague malaise, anorexia, occasional diarrhoea, and loss of weight for three months. For several weeks he had had night sweats and more recently rigors with fever up to 101°–104° F. (38.3°–40° C.). On examination he was a wasted, ill man. Temperature 102° F. (38.9° C.), pulse 96. His tongue was moderately coated. The liver was smoothly enlarged by three fingerbreadths, and the spleen was enlarged by two. There was no palpable lymphadenopathy. The heart, lungs, and C.N.S. were normal. He had old bilateral iridectomies.

His white cells numbered 2,400 per c.mm. (neutrophils 78%, lymphocytes 18%, Türk 4%), Hb 51%, red cells 3,730,000 per c.mm., colour index 0.68; Van den Bergh reaction was delayed; serum bilirubin 2.25 mg.%; thymol turbidity 2 units; serum colloidal gold 000000. Prothrombin index (Quick) 83%. Blood culture was sterile, and the urine showed only a trace of albumin. Chest skiagram normal and barium meal and follow-through showed no abnormality of the gastro-intestinal tract.

The patient went steadily downhill with fever up to about 102° F. daily. Needle biopsy of liver was contemplated, but in view of his condition was felt to be unjustified. No final diagnosis was reached and he died 18 days after admission, approximately six weeks after the onset of fever and three to four months from his first vague symptoms.

At necropsy the relevant positive findings were: scarring at the apices of both lungs with a few adhesions low on the left side: oedema and bronchopneumonia at the bases; enlargement sometimes with caseation of deep cervical, mediastinal, and retroperitoneal lymph nodes and less marked enlargement and lymph nodes throughout the mesentery; enlargement of the spleen with whitish, necrotic nodules up to 0.5 cm. diameter; enlargement and softening of the liver, which contained numerous smaller whitish areas; one small whitish nodule in the left kidney; apparent regeneration of the bone marrow of the right femur down to the junction of its lower and middle thirds.

Histologically the mediastinal and retroperitoneal lymph nodes were largely replaced by caseation with moderate lymphocytic and endothelioid cell reaction and an occasional Langerhans giant cell. Most of the splenic and hepatic lesions showed necrosis with an occasional giant cell but little or no round cell infiltration. The left kidney showed a small area of round cell infiltration. The apex of the right lung showed pleural thickening but no marked change in the lung tissue. The lesions in the lymph nodes, spleen, and liver contained a moderate number of acid-fast bacilli. This case would appear to resemble the anatomical form (*a*) described in the article. The lack of round cell infiltration and the abrupt change from normal to necrotic tissue were the predominant histological findings in the liver and spleen suggesting an inadequate reaction to the infection.

If his condition had permitted, liver biopsy would have seemed a logical method of arriving at the diagnosis. Our thanks are due to Dr. R. B. Terry, physician, and Dr. G. L. Robinson, pathologist, for facilities to publish this case.—We are, etc.,

S. R. GLOYNE.
Greenwich, S.E.10. R. KING-BROWN.

Serum Potassium Deficiency

SIR,—Dr. J. A. Strong (October 27, p. 998) has fallen into the common error of considering threshold voltage measurements a reliable indication of neuromuscular excitability.

The level of threshold stimulation depends on the two factors skin resistance and tissue excitability. Environment, skin preparation, and technique have been shown to have great influence on skin resistance, and hence on threshold measurements.[1 2 3] For

example, threshold values can be dropped by 10 volts by a change in skin temperature from 27° to 34° C. Muscle exercise, oedema, and alterations in local blood flow[3 4] can produce similar effects. Of even greater importance is the position of the stimulating electrode.[3] Threshold values increase as the electrode moves from the motor point, and in a bulky muscle like the quadriceps some skin marking of the position is necessary if comparable serial readings are to be obtained. Carefully standardized conditions must be used throughout, and even then a considerable variation may be found from day to day in the threshold values of normal muscle. A variation of 10 volts is well within normal limits.

The chronaxie[5 6] is a much more reliable measure of electrical excitability of muscle This expression takes into consideration both the threshold and the shape of the strength-duration curve. (The graph obtained by plotting threshold voltage against pulse length is known as a "strength-duration" or "intensity-time" curve.) The chronaxie can easily be read from such a curve, which can be obtained from the pulse duration available on the Ritchie-Sneath stimulator.

As a result of study of some thousand such strength-duration curves I have concluded that threshold voltages themselves, even using the most exacting techniques, are subject to wide variations and do not give a reliable measure of excitability. In contrast to this, the chronaxie is remarkably constant.

I have myself followed the electrical excitability of muscle in a small group of tuberculous subjects. The full strength-duration curves of fifteen muscles were plotted at monthly intervals for five months. Variations in threshold voltages were found considerably greater than those quoted by Dr. Strong—e.g., at 100 millisec. the range of threshold voltage was: subject H, 30–45 volts; subject P, 30–40 volts; subject R, 34–42 volts; subject S, 28–47 volts. The muscle used for these figures was the first dorsal interosseous, technically a simpler muscle to test accurately than the quadriceps. I may add that I consider these variations to be within the limits of normal, and that in these cases the excitability as measured by chronaxie was fairly constant.

As Dr. Strong does not give threshold values for pulse durations shorter than 0.1 millisecond, the chronaxie cannot be measured from his figures. I regret this, as careful observations on muscle excitability in a variety of pathological conditions are badly needed, and alterations in serum potassium concentration might well be expected to alter neuromuscular excitability.—I am, etc.,

London, W.C.1. R. HARRIS.

REFERENCES

1 Bauwens, P. (1941). *Brit. J. phys. Med.*, **4**, 150.
2 Ritchie, A. E. (1945). *Edinb. med. J.*, **52**, 289.
3 Harris, R. (1950). *A Study of Electrical Excitability of Muscle*. University of Leeds.
4 MacKenzie, I. (1948). *Strength Duration Curves in Poliomyelitis*. University of Edinburgh.
5 Bourguignon, G. (1932). *La Chronaxie Chez l'Homme*. Paris.
6 Lapicque, L. (1926). *L'Excitabilité en Fonction du Temps*. Paris.

Liver and Brain

SIR,—In their paper (November 3, p. 1054) Dr. A. G. W. Whitfield and Professor W. Melville Arnott have posed, once again, the problem of the relationship between the liver and the brain, and have suggested that recurrent attacks of coma in cases of cirrhosis "may arise from factors similar to those which operate in Wilson's disease." Undoubtedly, whenever neurological phenomena make their appearance during the course of a chronic liver disease the question of some underlying analogy with hepato-lenticular degeneration comes to mind. But it is perhaps misleading, and quite possibly fallacious, to suppose that this analogy can be carried any further than the mere fact of a liver–brain relationship. Certainly the factors responsible for such a relationship, in Wilson's disease, are not yet precisely known. But, whatever they may be, it is highly probable that they are of a unique character and could not therefore be invoked as a universal explanation for other instances of coexistent liver and brain pathology. No more so, indeed, than the cerebral changes of kernicterus can be said to provide any clue to this relationship, as Wiener and Brody (1946) have pointed out.

There exists, in the literature of various countries, a large selection of case reports in which chronic liver disease has been associated with a variety of cerebral changes, evidently of a secondary nature. Some of these approach very closely to Wilson's disease in their clinical and pathological manifestations (Schaltenbrand, 1926; Waggoner and Malamud, 1942; etc.). And certain authors have considered it desirable to visualize a broad category which would embrace not only hepato-lenticular degeneration but also all these other disorders within a single comprehensive terminology—e.g., "hepato-cerebral degeneration" (Brouwer, 1936, and others), or "neurohepatic degeneration" (Fracassi, 1944).

Nevertheless one feels that the bringing together of such a widely assorted variety of syndromes merely adds confusion to a situation already sufficiently vague. To this it could be added that the interdependence of liver and brain lesions in Wilson's disease has not yet been proved beyond all possibility of doubt. There are, for example, a number of case reports which give rise to the suspicion that the pathological changes in the brain can occur in the complete absence of demonstrable hepatic damage, either clinical or histological (e.g., Jervis *et al.*, 1942). Admittedly, however, this is not a widely accepted theory.

Finally there is, in Wilson's disease, the question of disturbances in the metabolism of copper and amino-acids, which clearly set this malady apart from all other varieties of hepatic cirrhosis (with the exception of the Fanconi syndrome, which is not relevant to the present matter).

Thus, however closely certain other morbid states may have fortuitously resembled it, one may take leave to doubt whether there is any similarity in the underlying mechanism of the disease process.—I am, etc.,

Newtownards, Co. Down. C. G. WARNOCK.

REFERENCES

Brouwer, B. (1936). *Proc. roy. Soc. Med.*, **29**, 579.
Fracassi, T. (1944). Abstracted in *J. Amer. med. Ass.*, **124**, 130.
Jervis, G. A., *et al.* (1942). *Psychoanal. Quart.*, **16**, 357.
Schaltenbrand, G. (1926). *Dtsch. Z. Nervenheilk.*, **91**, 174.
Waggoner, R. W., and Malamud, N. (1942). *J. Nerv. ment. Dis.*, **96**, 410.
Wiener, A. S., and Brody, M. (1946). *Amer. J. ment. Defic.*, **51**, 1.

Alcoholism

SIR,—It is stated in your annotation (November 10, p. 1139) that according to W.H.O. tentative estimates of numbers of alcoholics for various countries (*World Hlth Org. techn. Rep. Ser.*, 1951, 42) U.S.A. and Sweden have the highest proportional number of alcoholics, while Italy has the lowest. This is so according to column 6 ("estimated number of alcoholics with and without complications per 100,000 adults") of the table published by W.H.O., but not so according to column 5 ("estimated number of alcoholics with complications per 100,000 adults"), which is regarded by W.H.O. as the more reliable estimate. Column 5 reads as follows: Switzerland, 1,590; Chile, 1,497; France, 1,420; U.S.A., 988; Australia, 671; Sweden, 646; Denmark, 487; Italy, 476; Norway, 389; Finland, 357; England and Wales, 278.—I am, etc.,

Society for the Study of Addiction. H. PULLAR-STRECKER.

Kinder Anaesthesia for Children

SIR,—Provided the stomach is empty, I have found oral premedication is completely satisfactory and far more pleasant for patients. Premedication is given one hour before operation, employing "seconal," together with atropine and hyoscine kept as a ready-made solution of equal parts. Such a solution, if kept in a refrigerator, lasts 14 days in perfect condition. Using seconal, I find that hyoscine combined with atropine is ideal for its hypnotic action together with suppression of secretions, whereas seconal and hyoscine alone exert too depressant an action. The average dose for a child of 3 years is ¾ gr. (48 mg.) seconal and 1/200 gr. (0.32 mg.) each of hyoscine and atropine. For 5 years the seconal is increased to 1¼ gr. (96 mg.); for 7 years 1½ gr. seconal and 1/150 gr. (0.43 mg.) each of atropine and hyoscine.

For induction I use ethyl chloride in the ward: the child need not be wakened as long as the cold mask is not allowed to touch its face.

For giving thiopentone I find the following method to be almost or completely painless. Apply tourniquet lightly, leave *in situ* for two to three minutes, rubbing the antecubital fossa well with 2% "cetavlon"; then inject with

a fine sharp needle. Cetavlon has a distinct advantage over spirit in making the palpation of a vein infinitely easier; a trace of spirit carried with the needle to the cutaneous nerve endings is definitely painful.

Also, I would humbly remind others that I invariably tell children (over, say, 7 years) that of course it is quite impossible for them to wake up during the operation. This fear I haye found on questioning to be very common—it caused me as a child to resist to the uttermost the efforts of an anaesthetist to induce me.—I am, etc.,

Umtali, Southern Rhodesia. ANTONY M. GREEN.

Proper Use of Insecticides

SIR,—Dr. E. H. Eason in commenting (November 3, p. 1088) on my letter on this subject reproves me for an assumption which I did not make. That there is evidence of resistance being recessive and that there is evidence of loss of resistance on further breeding in absence of the adverse factor are two statements both of which are true independently. I regret if in making these two brief statements in one sentence I have misled any of your readers. In view of your annotation (p. 901) I should perhaps add that this reversion has been reported from field work as well as under laboratory conditions. As observed in your annotation, the genetical investigations give conflicting results, and although publication of the proceedings of the ninth International Congress on Entomology (Amsterdam, August, 1951) will provide more information the story is far from complete.

The point I wished to emphasize was that in practice the use of mixtures of insecticides should not be recommended, and where chemical control measures are being used it is advisable on present evidence to alternate treatment with different selected insecticides. In this connexion the remark in your annotation that a *return* to sanitation is advisable suggests that those using insecticides may have dropped general hygiene measures. If so I should strongly support your comment, because it is fundamental that the use of insecticides should be supplementary to normal sanitation.—I am, etc.,

Imperial Chemical Industries, Ltd., Runcorn, Cheshire. F. P. COYNE.

Herpes Zoster Involving Anterior Horn Cells

SIR,—The report of Dr. J. H. McIntyre (September 22, p. 716) of his case prompts me to report the following.

On February 27, 1946, I was called to see a man aged 52 complaining of sciatic pain in his right leg. He gave a previous history of sciatica in 1930. Reflexes were normal, but I noted some hyperaesthesia in the leg and tenderness over his lumbar spine. By March 3 he had developed a typical herpes zoster rash on the leg in the distribution of L 5. On March 10 he complained of diplopia, and subsequently developed a complete foot-drop. His right knee-jerk was obtained only after reinforcing. The herpes cleared normally and all pain disappeared, with return of the knee-jerk, by the middle of April. The foot-drop and diplopia persisted. He attended hospital as an out-patient and received massage and faradism to his leg, and was fitted with a spring support to his foot. His foot-drop gradually disappeared, and by February, 1947, he had slight weakness in dorsiflexion of his right big toe only. His diplopia had gone by June, 1946. He had no other central nervous signs, and was completely apyrexial throughout his illness. He was considered to be a case of encephalomyelitis.

—I am, etc.,

Hawkhurst, Kent. J. A. J. HAMMOND.

Device to Measure Skin Temperature Gradients

SIR,—An investigation into the temperature gradients of the skin of the leg necessitated the estimation of the temperature at 16 areas with a minimum time lag between the readings. This was achieved in the following manner. Copper–constantin thermocouples, standardized against one another by adjustment of the area of contact between the wires of which they are composed, were connected through a mechanical switching gear (A.M. Distributor Type VII, Ref. No. 50/1065) to a sensitive galvanometer with a period of less than 1/50 sec. The mechanical switching gear closes 20 contacts in three seconds and the temperature gradient is

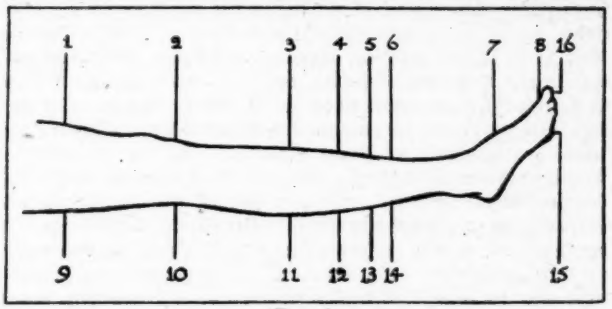


FIG. 1.

recorded on photographic paper moving at 4 cm./sec. The thermocouples are taped to the leg in the positions indicated in Fig. 1; one is in ice, another in air adjacent to the limb, and a third in water at about 40° C., providing reference levels from which the actual temperature of the limb may

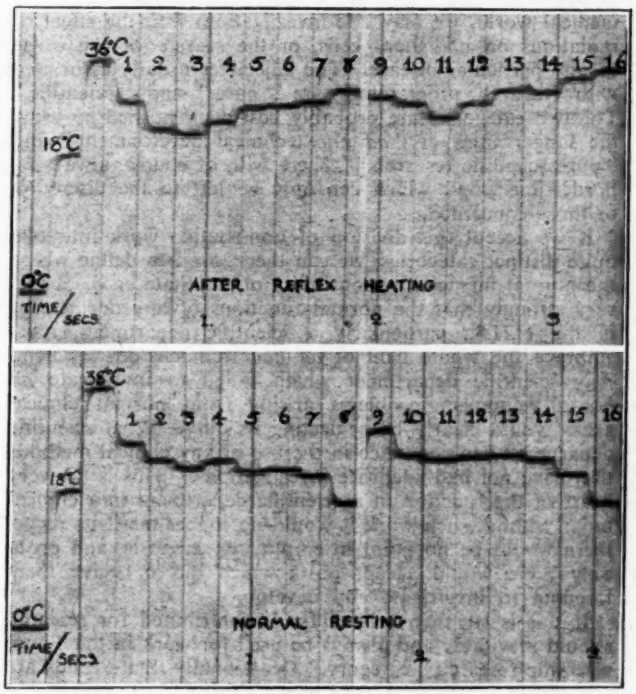


FIG. 2.

be estimated. A typical example is given in Fig. 2, which illustrates the change in the temperature gradient which follows reflex heating of a normal subject.

I am grateful for the technical assistance of R. L. G. Rainbow.

—I am, etc.,

Postgraduate Medical School, London, W.12. D. G. MELROSE.

Pure and Applied Research

SIR,—I should like to draw attention to the new importance the definition of "research" has acquired, now that nearly all medical work is State financed. It is necessary to be sure that private donations for research are used entirely for work outside the normal financial responsibility of the State and that the work is of the nature envisaged by the donor. Surely in such cases the donor intends that some extra work should be done and that his money should not merely be used to relieve the Exchequer of a part of the cost of running the Health Service. We should try to encourage donors and their representatives to clarify their meaning in presenting funds for research. This problem arises in dealing with gifts of money to various bodies in the N.H.S., but I am acquainted only with the hospital service, and even there, I am, of course, expressing purely personal opinions.

In order that we may be certain to make right decisions in such matters, it is highly desirable that a clear definition of the word research should be generally accepted. Unfortunately, one often hears the word used to cover anything which is outside the daily routine of a department. This is a loose practice, leading inevitably to misunderstandings. It would probably make for much greater clarity if non-routine scientific work were always divided into the two categories of development and research. These divisions are accepted by most scientists and the boundaries would be widely agreed. Surely it is true to say that development covers all investigations of an *ad hoc* nature and relates to improvements rather than discoveries, to applications of known principles rather than the discovery of new principles. As instances of development work we may cite the design of new instruments for measuring doses in radiotherapy. In fact the adjectives "*ad hoc*" or "technical" are usually associated with development programmes. On the other hand, surely it is true to say that research should cover all investigations which seek the discovery of new principles, or inquiries which seek new truths about any facet of nature, be it physical, medical, physiological, or any other. As instances of pure scientific research in the medical world, we may cite investigations into the effect of radiations on malignant cells, or the search for the cause of any particular disease. The adjectives usually associated with research programmes are "pure" and "scientific." The two categories are probably best distinguished by using the longer titles of "*ad hoc* technical development" and "pure scientific research." There will, of course, always be border-line cases, which can only be left to the discretion of those concerned.

If we accept this division of non-routine work into two quite distinct categories, we can then go on to define where the normal financial responsibility of the State ends. I feel very strongly that the normal functions of any department in the N.H.S., particularly a scientific department, must embrace the whole field of *ad hoc* technical development. Any scientific department which failed to investigate *ad hoc* development problems arising from normal clinical needs would clearly be neglecting its duty. What scientific department can acquiesce in the use of any clinical methods that have not had adequate investigation? This is the very heart of the function of a scientific department in a clinical unit: without such work it would no longer merit its name, there would be no point in employing scientists, and probably none would accept posts which did not give them freedom to investigate and develop.

If this is so, then private funds contributed for research should inevitably and always be used for work in the "pure scientific research" category. Occasionally, State funds are earmarked for research, and here, too, the distinction should be clearly made.—I am, etc.,

Scunthorpe. DUNCAN D. LINDSAY.

Chronic Otorrhoea and Chloramphenicol

SIR,—Apart from the method of treating safe cases of chronic otorrhoea locally with chloramphenicol drops and wicks, as described by Mr. Roland S. Lewis and Dr. J. D. Gray (October 20, p. 939), the method of the insufflation of the powder has practical interest.

The contents of a chloramphenicol capsule is a fine light powder which is very suitable for insufflation; indeed, it is easy to produce all gradations between a fine powder cloud and a heavy deposit by the gentle manipulation of a suitable insufflator—e.g., a small glass insufflator. In this connexion it is noteworthy that the capsule itself, punctured at each end and inserted into the end of a rubber tube attached to a hand bulb belonging to an atomizer or Politzer bag, makes a good insufflator; if any blocking should occur during insufflation, the capsule may be reversed in the tubing During insufflation the powder cloud can be directed accurately along an ear speculum after the ear has been cleaned of discharge—e.g., by dry mopping. This is an easy and quick procedure and, in my experience, need only be carried out on a few occasions to produce a satisfactory result in the majority of cases. I usually treat my cases about twice a week by this method, but it is not unusual in my experience for one application of the powder to produce a dry ear. Indeed, it does not seem so surprising that a powerful antibiotic powder in a highly concentrated form which remains *in situ* should exert a rapidly sterilizing effect in the presence of a local, accessible infection.

Owing to the wide therapeutic range of systemically administered chloramphenicol, including its strong antibiotic action against such organisms as *Bact. coli*, *B. proteus*, and *Ps. pyocyanea*, which organisms are in many cases the important factors in troublesome and persistent otorrhoea, it would appear that when the infection is inaccessible or particularly heavy it would be worth while combining systemic and local chloramphenicol therapy in these cases, in the earlier stages of treatment.

I referred in the *Lancet* (July 28, p. 178) to the possibility of allergic reactions with local chloramphenicol therapy in chronic otorrhoea. In order to minimize this possibility insufflation of chloramphenicol should not be carried out too frequently nor over a prolonged period. In cases with an allergic diathesis any excess of the powder should be removed by an air douche—e.g., rubber ball syringe—and the powder can be rendered less likely to cause sensitivity by the addition of a bland dusting powder—e.g., pulv. zinci oxidi et amyli—which can be dusted over the surface which has already been covered by the chloramphenicol powder.

Lewis and Gray refer to the possible extension of local chloramphenicol therapy in other surgical conditions; in this connexion it is worth recording that I have found it of use in the following ear, nose, and throat conditions:

Submucous resection: insufflation of the powder between the flaps.

Maxillary sinusitis: lavage of the antra with a saturated solution of chloramphenicol.

Radical maxillary operation: insufflation of the powder into the maxillary antrum.

Chronic frontal sinusitis: sinusotomy and needle-puncture irrigation. This simple treatment was designed for local chemotherapy in cases of chronic frontal sinusitis which did not resolve with other conservative treatment. It has proved effective with various antibiotics and recently with chloramphenicol The treatment consists in doing a limited sinusotomy to evacuate exudate and polypi and to allow the application of antibacterial agents to the intra-sinus surfaces—e.g., by light insufflation; later, needle-puncture irrigation with an antibacterial solution is carried out, via the operation scar, if necessary. Apropos of this treatment, when infection of the sinus is by Gram-negative organisms, chloramphenicol should prove especially effective.

Ozaena: limited benefit, in three cases, by douching with a saturated solution once or twice a week, and cleansing with oil and occasional insufflation of the powder. The improvement in these cases was indicated by the reduction of exudate and the suppression of the offensive odour. It cannot be denied, however, that the improvement, in a greater or lesser degree, may have been due to the mechanical cleansing of the nose. In one case the treatment was carried out in conjunction with the topical application of another chemotherapeutic agent.

Bronchoscopy in bronchial infections: insufflation into the bronchi, via the bronchoscope. Incidentally, the cloud produced by insufflation is so fine and penetrating that it might well have a place in inhalation therapy—e.g., in infections of the respiratory tract.

Fenestration and mastoid surgery: insufflation of the powder is of use in preventing sepsis and promoting healing.

In conclusion it may be said that chloramphenicol is a useful agent in the topical chemotherapy of certain E.N.T. conditions. If necessary, systemic and local therapy can be combined, and at times it may be advantageous to use chloramphenicol in conjunction with other antibacterial agents.—I am, etc.,

London, W.1. W. H. B. MAGAURAN.

Adjusting pH of Colloidal Gold

SIR,—In the preparation of colloidal gold sols for the Lange reaction, the lengthy process of tube titrations with serial dilutions of hydrochloric acid has been avoided by using a potentiometric *p*H apparatus. The quinhydrone-saturated calomel electrode system was used in conjunction with a millivolt bridge potentiometer.

A representative sample of colloidal gold sol was prepared with sodium citrate and hydrogen peroxide (Gradwohl, *Practical Laboratory Methods and Diagnosis*, 1943, vol. 1, p. 867), titrated with acid and edestin to the desired sensi-

tivity (Stitt, *Practical Bacteriology, Haematology, and Animal Parasitology*, 1939, 9th ed., p. 637), and checked with a known paretic C.S.F. to give a first-zone reaction. A sample of this sol was then incorporated in the quinhydrone-saturated calomel electrode system and the resulting potential difference across the two half-cells read on the millivolt bridge, which had previously been calibrated against a standard Weston cell.

Further gold sols were then made up using the same technique, and 100 ml. samples were titrated with N/5 HCl, after cooling, in the potentiometric apparatus until the potential difference under the same conditions became the same as that due to the standardized sample. The quantity of N/5 HCl to be added to the full batch of gold sol was then calculated. The gold sol was then set up in comparative series with the standard sol, using edestin, known first-zone C.S.F., and known negative C.S.F. The reactions of the two gold sols were identical.

The conclusions drawn from this are that a colloidal gold sol can quickly and accurately be brought to the correct *p*H for use; and that that *p*H can be checked at any time if required. It is wise, however, since the *p*H is only one of the factors affecting the sensitivity of the sol, to set up each *p*H-corrected batch with a known C.S.F. or with edestin in order to determine its usefulness. It is not possible to quote any "correct" *p*H value for a gold sol, since this will vary with different conditions; the optimum *p*H in this laboratory is 3.2, a value which was arrived at by means of the equation for the system:

$$pH = \frac{E_0 - E_1 - E_{st}}{0.059} \text{ at } 25^\circ \text{ C.}$$

where E_0 = electrode voltage referred to the hydrogen electrode, corrected.
E_1 = observed potential difference across the whole system.
E_{st} = potential difference due to the saturated calomel half-cell, corrected.

I am indebted to the Director of Medical Services, Northern Rhodesia, for permission to publish this letter.

—I am, etc.,

Lusaka, N. Rhodesia. KENNETH G. GADD.

Antihistamine and Spreading Factor

SIR,—In your annotation on "Hyaluronidase as a Research Tool" (November 17, p. 1204), reviewing the reports by Drs. Holborow, Keech, and Bywaters, you bring attention to the possible influence of vascular responses on the action of hyaluronidase. This possibility is supported by the finding that antihistaminic drugs, which influence vascular responses, can inhibit the spread of dye in the skin of animals by hyaluronidase (Mayer, R. L., *Ann. N.Y. Acad. Sci.*, 1950, **50**, 1127). This was confirmed in man (Pepys, J., *Acta Allerg. Kbh.*, 1951, **4**, 115), and in addition it was found that the injection of adrenaline into the skin also has the effect of localizing the indicator superficially. Fluorescein was used as indicator (and did not completely inhibit the action of the hyaluronidase), and under ultra-violet light the dye appeared as a vivid, intense patch of colour with an increased area of spread as compared with controls. Both drugs influence vascular responses, and in the case of the adrenaline it was felt that the vasoconstriction retained the dye and enzyme more superficially. The antihistaminic drug inhibited the vascular inflow, which may otherwise have dispersed the enzyme and dye and increased the spread.

The wealing reaction produced by hypersensitivity to hyaluronidase leads to an enhanced rate of disappearance of the indicator and can be explained not only by potentiation of spread of the enzyme by the increased intradermal pressure due to the oedema as suggested by the authors, but also by wealing *per se*, which is capable of producing the same result.

Abrahamson and Engel (*J. invest. Derm.*, 1938, **1**, 65) showed that histamine and allergic weals enhance very considerably the disappearance of a variety of dyes from the skin. Fresh blood and blood pigment were affected in the same way and can disappear within half an hour or less of the production of a histamine or allergic weal. This has been confirmed (Pepys, 1951), and, as is to be expected, this action of the weal is inhibited by antihistaminic drugs and also by adrenaline. Interference with vascular responses plays a part here as well.

These comments have some bearing on the technical aspects of the tests described, and are presented for that reason.—I am, etc.,

Institute of Laryngology and Otology, W.C.1. J. PEPYS.

Value of Estimating Urinary Chloride

SIR,—I read with great interest the Refresher Course article (November 17, p. 1207) by Dr. D. A. K. Black on "Water and Electrolyte Depletion." In the section on biochemical tests in diagnosis I was surprised to find no mention of the quantitative test for chloride in the urine. The section was wholly devoted to various estimations of the plasma electrolyte concentrations; but, in the author's words "it sometimes happens that concentrations of electrolytes give a false picture of electrolyte balance in the body." It is surely for this very reason that *urinary* chloride estimations have been used in the past. If the urine contains much salt and is of low volume, then the body lacks water; but if it contains no salt and its volume gradually falls, then salt is needed. This may be an oversimplification, but I believe that it is a useful guiding principle, and perhaps more reliable than the estimations of the plasma electrolytes recommended by Dr. Black. In this I may be mistaken, and no doubt others will write and tell you so if I am. But in the convenience of the test there can be no doubt that the urinary estimation is far superior. It can be done by the general practitioner (to whom Dr. Black's article was addressed) in his surgery, and with the simplest equipment. The plasma tests involve the tiresome sterile technique of blood-letting, and the delays of sending the samples for laboratory testing.

The simpler of two procedures is often used by general practitioners solely because it *is* the simpler, but in this case I suggest that it is also preferable on purely medical grounds.—I am, etc.,

Heronsgate, Herts. G. F. B. BIRDWOOD.

Deafness from Dihydrostreptomycin

SIR,—With regard to the recent correspondence on this subject (September 15, p. 651, and November 17, p. 1221) an explanation may be found in the dosage and mode of administration of this drug. Thus Carr and others (*J. Amer. med. Ass.*, 1950, **143**, 1223) from the Mayo Clinic, in analysing the neurotoxic reactions of 10 patients, found that in nine there was direct or circumstantial evidence that the maximum concentration of dihydrostreptomycin in the blood serum was greater than 60 micrograms per ml. Such concentrations may be avoided by administering only 1 g. dihydrostreptomycin every 12 hours to an adult provided renal function is normal. Hinshaw (*Amer. J. Med.*, 1951, **9**, 654) has discussed this problem and concludes, "There is at present no convincing evidence that either streptomycin or dihydrostreptomycin is more toxic to the auditory function of the eighth nerve than is the other drug."—I am, etc.,

Heanor, Derbyshire. R. N. JOHNSTON.

"An Alcoholic Wife"

SIR,—The note by your medico-legal correspondent (November 10, p. 1160) on this topic contains the statement, "Mr. Commissioner Blanco White found in the case before him that the wife had had no intention to drive her husband out of the home, and that therefore she had not deserted him." This is not the law, and it must be assumed that the Commissioner was incorrectly reported.

In *Boyd* v. *Boyd*, 1938 (4 All E.R. 181), Lord Justice Bucknill said (with regard to constructive desertion), "It seems to me that the essential element in desertion must be the intention to bring cohabitation to an end."

In *Edwards* v. *Edwards*, 1948, p. 268, The Divisional Court, Lord Justice Merriman said: "I think that that judgment is wrong, and that we are not bound by it, and as this case [*Boyd* v. *Boyd*] is constantly being cited to us, we are not merely entitled, but bound, to say so. I have mentioned the fact that this court, and, indeed, many judges in the Division individually, have referred over and over again to the principle that a man must be taken to intend the natural consequences of his acts, and if it is a natural consequence of a man's direct treatment of his wife that she leaves him it is a commonplace that he must be taken to intend her to do so."

Mr. Justice Barnard said: "I agree with my Lord and I particularly agree with what he has said about the judgment of Lord Justice Bucknill in *Boyd* v. *Boyd*; in my opinion he has gone a little too far in requiring in a case of constructive desertion some definite evidence of a clear intention on the part of one spouse to drive the other spouse away."

The law therefore is as follows, "A spouse whose conduct amounts to turning the other out of doors is guilty of constructive desertion provided the fact of separation ensues. *It is no answer that such effect was not intended* (Kee and Cooper-Cole's *Divorce Case Book*, 1950, pp. 79–83).—I am, etc.,

Bristol. WALTER SIMPSON.

*** Our medico-legal correspondent writes: As a general proposition of English law, as Mr. Simpson is right in pointing out, there is a presumption that a man intends the natural consequences of his acts, and cannot be heard to say that he did not. If, however, it is shown that by reason, for example, of insanity he was not capable of forming a rational intention, or if by reason of duress he was forced to do an act the consequences of which he would have avoided if he could, the presumption may be rebutted. The Commissioner held that by reason of her state of alcoholism the wife was in such a mental condition that the presumption was rebutted.

General Practitioner and Fluorescein Test

SIR,—At this time of the year particularly the ophthalmic surgeon sees the usual batch of cases of herpes corneae which have been diagnosed and treated as conjunctivitis. It would seem as if the general practitioner does not fully realize the importance of using the fluorescein test in any case of red eye before making a diagnosis. There should be no exception to this rule, as the procedure is extremely simple. A drop or disk of fluorescein is put into the conjunctival sac and the excess of stain washed out with tap-water or saline by means of an eye-dropper. The herpetic affection may then show itself as a single branching or dendritic ulcer, or as multiple staining spots in the corneal epithelium. These can be detected with the naked eye in most cases, but more definitely with the aid of a magnifying-lens or loupe.

The diagnosis is important, as the ulcer spreads over the surface, and if it invades the pupillary area treatment becomes much more difficult and tedious and vision may be permanently affected by scarring.—I am, etc.,

London, W.1. O. GAYER MORGAN.

Rh Factor and Congenital Deafness

SIR,—An investigation is being made into the association of Rh factor incompatibility and congenital deafness. It would be of great assistance to be able to examine twins—one affected with congenital deafness and one unaffected. If readers know of such twins who are willing to have blood Rh tests, would they kindly forward the names and addresses to the Neuro-psychiatric Clinic, Metropolitan Ear, Nose and Throat Hospital, 14/16, Granville Place, London, W.1?—I am, etc.,

London, W.1. KENNETH HAZELL.

Prevention of Common Ailments

SIR,—It is always of interest in reading the contributions to the *Journal* to see what advice, if any, is given on the prevention of the diseases and defects described. There must be a great fund of knowledge possessed by experienced practitioners on the prevention of common ailments; ailments which, if neglected, can lead to more serious trouble and which in turn may require hospitalization and expensive remedies. Several practitioners in this area have made suggestions of interest for the prevention of certain disorders, such as varicose veins, haemorrhoids, etc. There may be other practitioners who might care to send information of this type, whose experience might otherwise go unrecorded. If there are any such practitioners, I shall be glad if they will get in touch with me.—I am, etc.,

J. L. BURN,
Salford, Lancs. Medical Officer of Health.

Landmarks in Long Lives

SIR,—In the course of study of the biology of the ageing process I have been trying to assemble data on the identifiable landmarks in the growth-cycle of long-lived human beings. I would be most grateful to receive help from anyone who has records, or who would be willing to collect information, from which I could determine the mean age at menarche and at menopause in a group of women who have reached the age of 80 or more. Some patients may be able to provide the information from their own memory. There may also exist case records which would be analysable. If anyone could provide such data, even for a few cases, I would be obliged if he or she would communicate with me.—I am, etc.,

ALEX. COMFORT,
University College, W.C.1. Nuffield Research Assistant.

POINTS FROM LETTERS

Tuberculosis

Dr. S. G. TIPPETT (Itchingfield) writes: With a change in Government and a new Minister of Health it is clear that now is the time for the profession to renew its appeal for a thorough overhaul of our tuberculosis service. Let the Ministry of Health, as a start, publish all the facts about it, so that the public can learn the truth about its value. . . . For every case of tuberculosis notified and admitted into a sanatorium for treatment must we admit that a cure is only very remotely possible? . . . Are there no cases where the disease has been definitely permanently arrested; is there no information or list of permanently arrested cases published by the Ministry? . . . There are many factors that have a definite bearing on this problem, but there are two urgent factors that should receive immediate consideration. The first one is the problem of the prevention of infection by the tubercle bacillus. Can the resistance of the human body be built up by B.C.G. to resist infection, and, if it can, then for how long? The other problem is that of preventing the infection by the tubercle bacillus going on to the stage when it can be recognized as a case of tuberculosis.

Teaching Deaf Children at 18 Months

Miss S. M. MARTIN (London, S.E.4) writes: It seems insufficiently widely known that the training of deaf children can, and should, be started at a much earlier age than 5. At the Metropolitan Ear, Nose, and Throat Hospital, Granville Place, and one or two other London hospitals, deaf children are accepted from the age of 18 months. They attend twice a week and are taught to lip-read and to talk, and the residual hearing is stimulated and trained. The mothers are also trained to help their children at home, and periodic parents' classes with demonstrations and quarterly parents' meetings are held. This early training lessens the period of frustration for the child—many at the age of 2 to 3 years, even if not speaking, can lip-read many words—and considerably cheers and encourages the parents.

College of General Practice

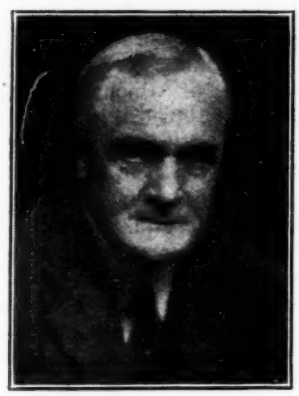
Dr. K. M. HAY (Birmingham) writes: . . . I suggest that a College of General Practice should interest itself in the wider aspects of medical history and philosophy, that it should have close association with the humanities, and that it should concern itself with defining the role that medicine could and should play in maintaining social cohesion and stability in an age of anxiety and change. If higher degrees are important, the thesis should be an essential element, as demonstrating an ability to form coherent systems of thought on current problems. . . .

Obituary

GEORGE L. CHIENE, M.B., F.R.C.S.Ed.

Mr. George L. Chiene, the well-known surgeon and teacher, died suddenly at his home in Edinburgh on November 19, aged 78.

George Lyall Chiene, son of the late Professor John Chiene, was educated at the Edinburgh Academy, Christ's College, Cambridge, and the University of Edinburgh, where he graduated M.B., C.M. in 1897. As a student he played a prominent part both in sport and study. Carrying on the traditions of his distinguished father, he took up surgery as a career. In 1901 he became a Fellow of the Royal College of Surgeons of Edinburgh, and was appointed to the staff of the Royal Hospital for Sick Children. Two years later he became an assistant surgeon to the Edinburgh Royal Infirmary, on the honorary staff of which he served for 34 years, being promoted to surgeon-in-ordinary in 1922 and senior surgeon in 1928. On his retirement in 1937 he was made consultant surgeon, and he also served as a member of the board of management. Both the Royal Medical Society of Edinburgh and the Medico-Chirurgical Society of Edinburgh elected him as their president.



During the South African war he served his country as an assistant surgeon in the Edinburgh and East of Scotland South African Hospital, and in the first world war as a major in the British Expeditionary Force in France. In the last war he returned from retirement and again gave his services in one of the convalescent homes attached to the Edinburgh Royal Infirmary.

Mr. Chiene was a general surgeon of wide interests and made contributions to the literature on a variety of subjects, including descriptions of a method of exposing the appendix and an operation for inguinal hernia. In 1904 he introduced spinal "stovaine" in Edinburgh. His *Handbook of Surgery* was first published in 1923. He was an outstandingly good teacher. His clinical lectures were prepared and delivered with conscientious care and enlightened by his artistic skill. He taught the value of a kindly word and a gentle hand in the examination of the patient, and excelled at putting everyone at their ease, his genial Scottish humour and knowledge of the vernacular contributing in no small measure to this. Attendance at his clinical lectures was for his students more a pleasure than a duty to be duly performed. He invariably treated the members of his firm as colleagues in a common field, and bridged the distance between student and teacher with a friendship which was real. This atmosphere was particularly appreciated by the younger students fresh from the systematic classroom and beginning to feel their way in hospital. A notable feature of his teaching were debates, at which he presided, on surgical topics each term. On such occasions even the most reticent student would speak with fluency, and there is little doubt that under his inspiration the students worked as hard to prepare for these debates as for many an examination. He never talked down to his students, but educated them in the truest sense.

Though his days were fully occupied he found time to cultivate many other interests. Painting was one of his recreations, and he was a skilful angler and golfer. Above all he was a great gentleman. Those who were privileged to be his assistants remember him with deep affection and gratitude.

Mr. Chiene is survived by his wife and two sons, to whom our sincere sympathy is extended.—J. R. C., J. A. R.

WILBUR A. SAWYER, M.D.

Dr. Wilbur A. Sawyer, whose death at the age of 72 is reported from Oakland, California, was well known throughout the world for his researches on yellow fever and other tropical diseases. As a member, and later Director, of the International Health Division of the Rockefeller Foundation, as well as a director of Unrra, he must have been personally known to countless medical men in every continent.

Dr. Sawyer came of an old New England family, of English descent, and was born at Appleton, Wisconsin, on August 7, 1879. He took an arts degree at the University of California, and then migrated to Harvard, where he graduated M.D. in 1902. After holding a house appointment at the Massachusetts General Hospital he joined the staff of the University of California medical school, becoming lecturer and later professor in hygiene and preventive medicine. During this period, in 1915, he made the fundamental discovery, the importance of which at the time passed unrecognized, that virus could be detected in the stools of patients with poliomyelitis.

In the first world war Sawyer served in the Medical Corps of the U.S. Army with the rank of lieutenant-colonel. One of his regrets was that he never saw service in France. However, he did much to control venereal disease in the American armed Forces. In 1919 he joined the International Health Board of the Rockefeller Foundation, and shortly afterwards went to Australia as director of the Foundation's hookworm campaign. His services were so much appreciated that he remained in Australia for a further two years as adviser in public health to the Australian Ministry of Health. During this time his only son was born, and he was rather pleased at pointing out that his son was *ipso facto* a British subject by birth. For two years, 1923–4, he was a director of the Rockefeller International Health Division in the East, and then he returned to America, where he became director of the public health laboratory service and, in 1927, associate director of the International Health Division of the Rockefeller Foundation. In 1935 he succeeded General Russell as Director of the International Health Division, a post he retained till 1944, when he became Director of Health to Unrra. He had been convener of the Section of Viruses and Viral Diseases at the Third International Congress of Microbiology in 1939, and much of the success of the Fourth International Congress of Tropical Medicine and Malariology held at Washington in 1948 was due to his work as secretary general.

Sawyer received many honours and awards. In 1945 the University of California made him an LL.D. He was a Knight of the Norwegian Order of St. Olav. The League of Nations awarded him the Leon Bernard Prize, and the American Society of Tropical Medicine, of which he became president in 1943, the Richard P. Strong medal. He was a member or fellow of many societies, including the Royal Society of Tropical Medicine.

Sawyer's most original work was carried out while he was in charge of the New York yellow-fever laboratories of the International Health Division of the Foundation from 1928 to 1935. In 1931, together with the late Wray Lloyd, he devised the intraperitoneal mouse protection test, by means of which it was possible to show the extension of yellow fever in time and space. He also organized the machinery by which sera were collected from persons in different age groups all over the world. Again with Wray Lloyd, he showed that it was possible to obtain a solid immunity against yellow fever in man by subcutaneous injection of the neurotropic strain of yellow fever discovered by Max Theiler, the tendency of the virus to localize in the central nervous system being prevented by injection of 0.5 ml. of human immune serum per kilogram of body weight. The writer of this note well remembers wishing, after Dr. Sawyer had injected what seemed pints of immune serum into his abdominal wall, that he had lived on a weight-reducing diet before going to America. Although this method of immunization obviously could not be applied to large numbers at any one time, it is well to remember that when applied to laboratory workers it abolished the long sequence of infections which had rendered working with yellow fever a matter of such danger. Apart from these outstanding investigations of his own, it must not be forgotten how large a part Sawyer also played in planning the whole campaign against yellow fever. No detail was too small and no task too great for him; his kindness and hospitality also were unforgettable. He was a tireless traveller, and after the longest and most fatiguing journeys, of which he made many, he would be as full of ideas and conversation as ever. He possessed idealism and all the highest qualities of the New Englander, combined with the knowledge and *savoir-faire* of a true man of the world. His many friends in this country will wish to express their deepest sympathy with his wife, son, and three daughters. One of his daughters was well known in London during the war years, when she acted as personal secretary to the American Ambassador, Mr. Winant.—G. M. F.

C. C. P. ANNING, C.B.E., M.R.C.S., D.P.H.

Dr. C. C. P. Anning, chief medical adviser to the Social Services Department of the Transvaal Chamber of Mines, died suddenly at Johannesburg on October 12, aged 51.

Charles Clifford Paul Anning was the eldest son of Dr. J. J. Anning, of Leeds. After leaving Cambridge, where he took the Natural Science Tripos in 1920, he continued his medical studies at Leeds, where he qualified in 1923. A year later he took the D.P.H. and began a distinguished career in public health as assistant medical officer of health of Dewsbury and later of Leeds. In 1926 he went out to Shanghai, where he had experience of a cholera epidemic. After a short period as assistant port medical officer in Liverpool, he accepted a post in Rhodesia as a medical inspector of schools. He then moved to South Africa, where he was successively M.O.H. of Pietermaritzburg and Benoni. During these years he managed to find time to work energetically for the B.M.A., being honorary secretary of Natal Inland Branch and Midlands Division from 1934 to 1936 and chairman of the East Rand Division in 1938. He went as a representative to the Annual Meeting of the B.M.A. in Australia in 1935.

During the second world war Anning served from 1940 to 1945, first as lieutenant-colonel and later colonel and A.D.M.S. of the 6th South African Division in Egypt and Italy. He was awarded the C.B.E. and also the American Bronze Star. For the past five years he was medical officer in charge of the Social Services Department of the Transvaal Chamber of Mines, an appointment newly created in 1945. He had to organize the activities of this department without any local precedent to guide him, but he successfully accomplished this task and continued the work until his death. He was the leading spirit in establishing the National War Memorial Health Foundation, of which he was chairman. His excellent broadcasts, "Health Travel Talks," were given partly in support of the work of this Foundation. He also played a leading part in the South African National Tuberculosis Association. Among Anning's many public-spirited activities was his initiative in arranging training for non-Europeans as health inspectors. This work he started when he was medical officer of health for Benoni, and since then a number of trainees have qualified by examination as health inspectors. This was a new departure in South Africa, for previously no such opportunity was available to non-Europeans. Dr. Anning is survived by his widow and an adopted son.

THOMAS WALMSLEY, M.D.

Dr. Thomas Walmsley, Professor of Anatomy in Queen's University, Belfast, died at his home in Armagh on November 12, aged 62.

He was born at Bombay in 1889, the son of Thomas Walmsley, an officer in the Royal Indian Navy. From Greenock High School he went on to Glasgow University, where he graduated M.B., Ch.B. in 1912. After two years as a demonstrator in the anatomy department he became house-surgeon to Sir William Macewen, and in 1916 he proceeded to the M.D. degree, being awarded a gold medal for his thesis on joints. In 1918 he returned to anatomy as a lecturer in embryology, and a year later, when he was 30 years of age, he was appointed to the chair of anatomy in the Queen's University, Belfast, where he succeeded Professor Symington. He remained in office 32 years. During his time in the chair Walmsley wrote a *Manual of Practical Anatomy* in three volumes and the sections on the heart and the action of muscles in *Quain's Anatomy*. In addition, he was the author of 30 papers, which included seven on joints, three on muscles, five of archaeological and anthropological interest, and six in association with different surgeons. It would appear from this list that his life as an anatomist might be divided into three periods—pure anatomy, applied anatomy, and finally anthropology. In 1939 he published an "Anthropometric Survey of the Peoples of Northern Ireland" (with John M. Mogey) and in 1948 a "Report on the Human and Animal Remains of the Bann Estuary."

It has been said that professors might fall into one of four groups—teachers, workers, thinkers, and committee-

men—but Walmsley qualified for all groups except the last. Rarely did he attend faculty or academic meetings, as he felt that for him they were a waste of time. He lived in and for his department, was popular with the undergraduates, and took an interest in their athletic life. His "basket of bones" lecture will be remembered by many generations of students. His department was a haven of refuge for those graduates who were attracted to academic work, and from this group many ascended into lectureships and chairs in anatomical departments, while others obtained the F.R.C.S. and qualified for clinical appointments as surgical specialists. The appointment of Thomas Walmsley in 1919 to the chair of anatomy in Belfast was indeed a fortunate occurrence for that medical school. Deep sympathy will be offered to his wife and two children.—P. T. C.

Professor J. Henry Biggart writes: The death of Professor Walmsley is a great loss to the academic strength of the Queen's University. He was a brilliant teacher, with a sound philosophy and knowledge of educational aims and methods. Quiet and reserved in manner, he yet succeeded in getting to know every student who passed through his department. He brought to his teaching a certain attitude of mysticism, and few lectures failed to be embellished with some generalization of philosophic worth. Indeed, many of his students will remember him and his teaching long after they have forgotten the details of anatomy. If the function of a University is to think, then Walmsley was one of our best servants. Every lecture, every departmental decision, every discussion was a subject for thought, and he succeeded in stimulating others to go and do likewise. A great teacher, a faithful worker, an adopted but loyal son of this University, he has left behind him, amid regrets at a career untimely closed, the memory of a well-spent life. Sowing as he did beside many waters, he reaped the blessings of equanimity, of philosophic peace, and of the contentment born of great service.

Dr. ALBERT JAMES GILBERTSON died at Sunderland on September 19, aged 70. The son of Alderman J. J. Gilbertson, of Southwick, Sunderland, he was born in 1881. He graduated in medicine at Durham University in 1904, and after working as a house-surgeon at Monkwearmouth and Southwick Hospital he went into practice in Dundas Street, Sunderland, and continued there until his retirement in 1950. Gilbertson later became honorary surgeon to Monkwearmouth and Southwick Hospital, holding that appointment for many years. As a member of the R.N.V.R., he was mobilized in 1914 and served in a hospital ship until 1917, reaching the rank of surgeon lieutenant-commander. On his return his practice rapidly increased, and in 1923 he took into partnership Mr. H. B. L. Levy. This association continued until Mr. Levy was appointed surgeon to the Royal Infirmary. Gilbertson was also surgeon and Naval agent for the port of Sunderland and medical officer to the Lambton and Hetton Collieries, where the miners greatly respected his judgment and his fairness.

W. E. H. and P. A. write: "Gilly," as he was universally called, possessed great personal charm. He was essentially a man of simple tastes. He greatly enjoyed a cup of coffee with a friend, a chat about stamps, a talk about cars—he was about the first medical motorist in Sunderland. He radiated a kind of warm good-fellowship—you felt that you were the one person whom he had been most anxious to meet—and he had a host of friends. He had a very large practice and of all classes of patients—rich, comfortable, and poor. He looked after them all with equal regard and with equal care. His patients loved him; he controlled their health, their activities, and sometimes their conduct and finances. For some time he was a director of a shipbuilding firm. He had an extensive knowledge of the problems of an industrial town in good days and bad and his advice was always wise. In early middle age he developed rheumatoid arthritis, which sadly crippled his movements and gave him much pain. It was often difficult for him to work, to get about, and to drive his car. He had to give up his golf, to which he was greatly attached. Gilbertson endured many personal and private sorrows, but no one ever heard him complain. Over a year ago he developed a fatal disease which he bore with stoical courage, and he continued to see his friends almost to the end. With his family about him, he almost enjoyed that last year. The congregation attending his funeral service at Bishopwearmouth Church testified to the widespread and heartfelt sorrow at a loss which so many felt. To his sons, and especially to his daughter, Dr. Elizabeth Gilbertson, who left her post at Manchester to nurse him, we offer our deepest sympathy.

All those privileged to have met and known Major C. G. HORACE COLLIER GATES, or "C. G." as he was affectionately known to his friends, will have heard with regret of his death in London on October 25. He was one of the few surviving stalwarts of another era. The son of a medical man, an officer in the I.M.S., Gates left this country early in life and took an active part in any war he could possibly get into. His medals, or "gongs" as he called them, were legion; all of them were won on active service, that for Tel el Kebir and the Egyptian campaign in 1882 being the first. Among others were the medal for service during Reil's rebellion in Canada in 1885, when he acted as a dispatch rider in the North-west Mounted Police. In 1898 Gates was in Cuba with Theodore Roosevelt's Rough Riders. He held the record of wearing the medal for the Boxer Rising in 1900 between the Queen's and King's South African medals. In South Africa he was a scout and bodyguard for Field-Marshal Lord Roberts, C.-in-C. In the first world war Gates served with distinction in the Dardanelles and Salonika. In the last war, at an advanced age, he did strenuous and dangerous work as an air-raid warden in London, and was injured in the course of his duties. In his youth he was a cowboy in the old West, and while "on herd" did part of the memorizing of his medical studies. He graduated M.D. at Harvard University. In the Klondike, in the days of the gold rush, he was serving with the North-west Mounted Police. Previously he had helped in the capture of the Apache renegade, Chief Geronimo, and had taken part in Buffalo Bill's wild west show. Interested in science and neurology, he worked at University College Hospital, London, and at Queen Square with Sir William Gowers and other neurologists. For a time he was in practice in Welbeck Street. Gates was related to the Huxleys and to the Hon. John Collier, R.A., to whom he sat as a model. He gained three medals for saving life in a civilian capacity: one presented by the Royal Humane Society for saving life at sea, a decoration for rescuing spectators at the Paris Exhibition fire, and the Iron Cross (civil grade) for saving guests in a burning hotel at Frankfurt. This decoration was personally presented to him by the Kaiser. Interested in the Legion of Frontiersmen from its inception by Roger Pocock in 1904, he devoted most of his later life to its cause. His well-bemedalled figure attracted attention at many Legion parades. Quiet and reserved in his manner, he was himself an excellent raconteur, and it is to be regretted that he never wrote his memoirs.—R. V. S.

Dr. JOHN FREDERICK WOLSELEY LEECH, who was for over 12 years medical superintendent of Roundway Hospital, Devizes, died on November 5 at Devizes and District Hospital, aged 70. Born at Enniscorthy, Co. Wexford, Dr. Leech was educated at St. Columba's College, Ireland, Warwick Grammar School, and Trinity College, Dublin. He graduated M.B., B.Ch. in 1904, and proceeded M.D. four years later. He took the D.P.M. in 1927. In 1905 he went

to Roundway Hospital, Devizes, becoming assistant medical officer to the late Dr. J. I. Bowes, whose daughter he later married. During the 1914–18 war Leech was a captain in the R.A.M.C., serving in France, Gallipoli, the Balkans, and Palestine. In 1917 he was mentioned in dispatches. After the war he returned to Roundway Hospital, becoming medical superintendent in 1934, a post which he held until his retirement nearly 13 years later. A keen yachtsman in his youth, he remained a sportsman all his life and devoted a great deal of his time after he retired to his favourite pastime of horse-riding. Dr. Leech will be sadly missed by his friends, colleagues, and patients, and our sympathy is extended to his wife and two sons, one of whom is a doctor.

Dr. ERIC GARDNER died on November 14 at Weybridge, where he had practised for over 40 years prior to a breakdown in health in 1947. The third son of the late George Gardner, of Hackney, he was born in 1877. His paternal grandfather was Thomas Gardner, owner of the Globe Pleasure Gardens, and his maternal grandfather was Thomas Soames, owner of the East Indiaman *Elizabeth*, the first ship to enter St. Katherine's Dock when it was opened in 1928. Dr. Gardner possessed the *Elizabeth's* oak-carved figurehead until he gave it to the Port of London Authority. He was educated at Merchant Taylors' School and Caius College, Cambridge, where he stroked the first May boat. He then entered the London Hospital Medical School, where he was surgical scholar in 1903, graduating M.B. in 1904. After a resident appointment at the London Hospital and another at the Hospital for Sick Children, Great Ormond Street, he joined Dr. Chapple in practice at Weybridge in 1906. Soon after this the Brooklands motor track was opened close at hand, and Gardner became honorary medical officer. Thus he became familiar with motor accidents and their results, and was the inventor of the modern "crash-helmet," which has saved very many lives and countless injuries. In 1914 the R.F.C., as it then was, the forerunner of the R.A.F., took possession of Brooklands, and Gardner had a big share in the task of selecting pilots and weeding out those constitutionally unsuited for flying. In 1917 he took a commission in the R.A.M.C., serving in Salonika and in the Caucasus. In 1936 he retired from general practice to become pathologist to the Surrey coroner, and soon made a reputation in forensic medicine. Among several important cases, that which brought him most into public cognizance was the "chalk-pit murder" of 1946: to his insistence that this was not an accident but a murder was due the complete investigation which resulted in the conviction of the murderers. His breakdown in health not long afterwards is believed to have been due to the strain which this case involved. He was a vice-president of the Medico-Legal Society and had contributed several papers to the literature on medico-legal problems. While still in general practice he had been for many years a member of the local district council (and at one time chairman), and took a big share in the building of the new Weybridge Hospital, opened in 1928; of this he was governor and chairman of the contributory scheme up to the creation of the Health Service. He was also a Liveryman of the Drapers' Company. Archaeology was yet another of his many interests: he was a Fellow of the Society of Antiquaries and vice-president of the Surrey Archaeological Society. This hobby engaged him more and more fully after his retirement from practice in 1947. Dr. Gardner married in 1907 Dora Constance, daughter of H. J. Smith, town clerk of Lambeth, who survives him with two of their three sons: one son was killed as a fighter pilot at or near Alamein.

We record with regret the death in Glasgow on November 19 of SISTER MARIE HILDA, who was for over twenty years head of the Notre Dame Child Guidance Clinic in Glasgow. She was 74 years of age.

P. G. McG. writes: During her years in child-guidance work Sister Marie Hilda came in contact with many keen and omniscient young doctors, who left her clinic imbued with a healthy humility, and an abiding wonder that this tiny gentle figure could produce such energy in action, speech, and thought. She drove herself unsparingly and ruthlessly and used her gentle charm to exact the impossible from her friends and colleagues. When Sister seized one's hand and addressed one as "My dear" there was little one would not do for her—and much was asked. Presiding at clinical conferences, she was charitably deaf to one's more vapid theorizings, but quick to seize on the lowest murmur of anything that might be of use to her children. Never have I known any person so wholly dedicated to an ideal—to serve God by the succour of those children who by constitution or environment led an unhappy or restricted life. And never have I known anyone so dedicated whose passion was so cloaked in humour and gentleness. Her influence will live for many years, not only in those who were patients at the clinic, but in the lives of all unhappy children who came under the care of anyone trained at Notre Dame. Psychiatrists, teachers, parents, and children have lost an outstanding stimulus, teacher, and friend.

Medico-Legal

BROKEN NECK NOT DIAGNOSED

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Soon after 9 p.m. on the evening of August 18 a car containing three men overturned in Oldham Road, Manchester. One of them, a pipe-fitter's labourer, aged 33, was found by the police to be unable to stand when removed from the car, and was taken to the casualty department of Ancoats Hospital. He was very talkative on the way but rational, although he had plainly been drinking. He did not seem to be injured, but complained that he could not use his legs.

He was examined at about 10 p.m. in the accident-room by the surgical registrar. He was conscious and fairly rational but uncooperative and resented examination. He smelt strongly of drink. The registrar found no evidence of shock, bone injury, or abnormality of the central nervous system. He had superficial laceration of the face, but complained of no pain. The police officer with him, after finding he was still unable to walk, asked the surgical registrar if he thought he was fit to be put in a police cell, and was told it would be all right. He was then taken back to the police station and charged at 10.40 p.m. with being drunk and incapable. He had to be carried into the charge-room, and said to the inspector that he would be all right if he could use his legs. He was put to bed in a cell.

When his friends came to take him home early next morning he still could not stand, and as the effect of drink had worn off and the inspector decided there must be something radically wrong he was sent back at 8.30 a.m. to Ancoats Hospital by ambulance. He had to be carried in, and the officer with him explained that he said he had lost the use of his legs.

The surgical registrar examined him again at 11 a.m. He remembered nothing about the accident and made no complaint except that his legs felt weak and were of no use. Both the registrar and the house-physician who also examined him observed unaided movements of his legs and resistance to assisted movements of his legs and trunk. On examination of his sensory nervous system the only abnormality they found was that sensitivity to pin-prick was diminished in an area up to and over the chest. They found the spine clinically intact and the bladder and bowel functions normal.

It did not occur to the registrar to have him *x*-rayed or detained for observation, and he was accordingly discharged certified: "Fit for police custody. No organic disease or injury discovered." When he got back to the police station at 2 p.m. he said he felt no pain but seemed dead from the waist down.

He was sent home in a taxi. He was seen by his doctor next day, and admitted to Withington Hospital on August 21. There his condition was diagnosed after some difficulty as due to a broken neck. He died on September 5 from septic bronchopneumonia. At necropsy the spine showed a dislocation between the sixth and seventh cervical vertebrae, the intervertebral disk being pulped. There was a slight swelling on the spinal cord at this level, but no other naked-eye lesion.

To their verdict of accidental death the coroner's jury at the inquest added the rider that "there has been gross neglect on the part of Ancoats Hospital, and we suggest a revision of the accident-receiving section to prevent recurrence."

RUPTURED COLON

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The Court of Appeal recently allowed[1] an appeal by Crossley Brothers, Ltd., from a judgment of Mr. Justice Pearce at Manchester Assizes which awarded £800 damages against them in favour of an apprentice employed in their apprentice training school.

While he was working at a vice a fellow apprentice approached him from behind and placed a compressed-air pipe near his rectum. He then signalled to a third apprentice to turn on the compressed air. The result was that the boy suffered from a ruptured colon and severe shock. As Lord Justice Singleton said, he might, but for very skilful surgery, have died.

The appeal was allowed on the ground that the injury resulted from wilful misbehaviour by the other two boys, a wicked act which the company had no reason to foresee and for which accordingly it was not in law responsible. The other two boys were prosecuted, convicted, and punished.

[1] *The Times*, October 5.

Medical Notes in Parliament

Foot Deformity in Children

Lieutenant-Colonel W. H. BROMLEY-DAVENPORT asked the Minister of Health on November 22 if he would consider setting up an inquiry into the cause of the high incidence of foot deformity among children, with a view to making recommendations to prevent such deformity. Mr. H. F. C. CROOKSHANK told him that information on this matter was continually being collected and considered by existing authorities and preventive action being taken in several ways. He doubted whether any new and separate inquiry was needed.

Sheffield Health Centre

Mr. RICHARD WINTERBOTTOM on November 22 asked the Minister of Health if his attention had been called to the desire of the Sheffield Health Authority to establish a health centre in premises already provided in Firth Park, Sheffield. Mr. H. F. C. CROOKSHANK answered that discussions were proceeding with the British Medical Association with a view to settling a model form of contract for doctors in health centres which would, he hoped, solve some of the difficulties which had arisen on earlier schemes. The development of health centres must, however, be subject to the general limitations in respect of building work.

Pregnancy and Catholicism

Asked by Mr. J. REEVES on November 22 what directions he had issued to doctors and midwives employed in the National Health Service when they were required to make a decision on whether to save the life of the unborn child or the mother in cases of complications in confinement, Mr. H. F. C. CROOKSHANK replied, "None, Sir."

Foreign Doctors and Dentists

Mr. S. S. AWBERY asked on November 22 how many foreign dentists and doctors were domiciled in this country and unable to follow their profession. Mr. H. F. C. CROOKSHANK regretted that no figures were available. He added that foreign-trained dentists and doctors could be registered in this country if they could satisfy the criteria laid down by Parliament. The question of reviewing the arrangements applicable to dentists so as to facilitate registration was being considered.

Leeds.—The headquarters staff of the Leeds Regional Hospital Board has been reduced by one since March and 24 vacancies then existing have been left unfilled.

Regional Hospital Board Staff.—In England and Wales, regional hospital boards, boards of governors, and hospital management committees employed 29,078 administrative and clerical staff on December 31, 1950. Comparable figures are not available for dates before the introduction of the National Health Service.

Venereal Disease in Korea.—From November, 1950, to September, 1951, 2,570 British soldiers in Korea were treated for venereal disease.

Universities and Colleges

UNIVERSITY OF OXFORD

The special status of M.A. has been accorded to Professor Ancel Keys, Professor of Physiological Hygiene, University of Minnesota.

Professor J. C. Eccles, F.R.S., will deliver eight Waynflete lectures on "The Neurophysiological Basis of Mind" at Magdalen College, Oxford, on Fridays, at 5 p.m., beginning on January 25, 1952. The lectures are open to members of the University in academical dress and, if space permits, to the general public.

The Welsh Memorial Prize for Anatomical Drawing has been awarded to Donald O'Sullivan (St. Peter's Hall).

The Theodore Williams Scholarship in Pathology for 1951 has been awarded to Mr. Geoffrey Bennett (St. Edmund Hall).

UNIVERSITY OF CAMBRIDGE

Dr. W. Russell Brain, President of the Royal College of Physicians of London, will deliver the Rede Lecture in the Senate House on Wednesday, May 7, 1952, at 5 p.m. His subject is "Medicine and the Mind."

In Congregation on November 10 the following degrees were conferred:

M.D.—*D. E. Marmion, *D. MacG. Jackson, G. I. C. Ingram, J. M. Stansfeld, F. E. T. Scott, N. M. Mann, G. Sheers, J. C. Sloper, M R. Jeffrey, J. Lorber

M.B., B.CHIR.—*Mrs. Jean M. Weston.

*By proxy.

UNIVERSITY OF LONDON

Sir Archibald Gray has been re-elected Deputy Chairman of the Court of the University.

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies indicated in parentheses: Dr. R. E. Bonham-Carter (Institute of Diseases of the Chest); Sir Stanford Cade (Royal Cancer Hospital); Dr. Katharine G. Lloyd-Williams (Cheltenham Ladies' College).

The A. H. Bygott Scholarship has been awarded to Dr. Frank Summers; the Rogers Prize for 1951 to Dr. D. A. K. Black for his essay on "Sodium Metabolism in Health and Disease"; and the Sanderson-Wells (Junior) Prize to Gottlieb Lobe Money (Guy's Hospital Medical School) for his essay on "The Role of Cobalt and Copper in Nutrition."

The degree of D.Sc. has been conferred on Professor C. H. Gray, Professor of Chemical Pathology at King's College Hospital Medical School.

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1] *E. W. Evans, [1] [2]G. H. Hall, [1] [4] [5]D. H. Randall (University Medal), [1] *Anne Savage, [1] [2]W. B. Thomson, S. W. Albright, J. F. L. Aldridge, G. J. Allum, F. A. Almond, Katharine M. Baker, A. A. Bapty, J. Barnes, W. R. Barrow, D. B. Benazon, P. D. Bennett, J. C. Betts, Beatrice I. Bing, J. W.

Bishop, K. Biss, J. Boothman, R. W. Bowen, D. J. Bowerman, J. F. Bray, J. H. Briggs, H. P. Burrowes, J. Burston, R. H. G. Butcher, R. J. O. Catlin, L. R. Celestin, Rosalind I. Chamberlain, W. A. Chitty, T. H. Christie, J. W. Comper, P. E. Conen, C. B. Cook, K. V. Cooper, J. S. Cornes, D. D. Cracknell, M. J. Craft, Sheila M. G. Crosland, L. Crystal, J. L. Currie, P. J. Darlaston, I. F. Digby, M. L. Doel, R. Duffield, W. C. Duncan, D. J. Durcan, D. F. Eastick, R. L. Edwards, G. L. Evans, T. L. Evans, L. G. Fallows, D. M. Fanning, Stella Feldman, R. G. Fender, G. H. Fisch, Beryl C. Fisher, J. P. Flamank, G. P. Flew, E. S. Foote, H. K. Ford, Carol A. Foxell, Jean S. Franklin, Rosemary A. Fraser, Una de H. Freeston, J. C. Gazet, R. B. Gill, J. B. Glass, Agnes M. Glen-Bott, J. I. T. Glover, J. A. Gobert-Jones, H. Gold, J. F. Goyder, J. K. Guly, P. G. Haigh, J. A. S. Hall, C. O. D. Harman, Anna C. Harris, Luena H. Hatcher, D. B. Hawkins, J. M. Hayman, B. H. Helal, Ursula E. E. Henderson, M. U. Henry, C. A. Higgins, J. A. Hobbs, A. F. Hoffler, J. N. Hoffmann, J. B. Holland, Stephanie Holmes, H. F. Hope-Stone, J. B. Ingram, E. O. Jacobs, H. C. M. Jarvis, J. E. Jelinek, N. Joels, E. T. Johns, O. A. H. Johnson, R. J. R. Johnson, Audrey K. Johnstone, E. E. Jones, F. R. Jones, G. Karpusheff, N. Kaye, D. Kelleher, J. G. Kenney, D. G. Kibblewhite, Jane M. Kilvington, H. T. R. Koch, Beryl J. Lander, Frances-Joan Langford, P. F. P. Lansdown, Brenda M. Lee, D. Lennie, E. A. C. Lloyd, M. M. Lubel, Dorothy J. Lucas, J. Mackett, C. McKinna, Rona MacLean, L. K. Manning, F. M. Mansfield, A. F. Masson, F. J. N. Masters, A. G. May, W. May, A. McK. Middleton, A. P. Millar, D. M. Millar, Jean E. Moore, D. J. R. Morgan, R. N. Nauth-Misir, Mary Ogden, G. P. C. Orlay, P. H. Padwick, P. Papworth, C. M. Parkes, E. R. Parry, P. L. Pelmear, Rosalind M. Pettyfer, G. D. Phillips, G. Picthall, Audrey J. Price, Elizabeth M. Price, P. Rawson, R. G. Redhead, H. N. Reed, G. H. Rees, D. A. Riley, J. D. Robinson, E. J. Rolls, E. J. Ross, Elsie R. Rue, Everel C. Sankey, M. B. Scott, Eileen M. Selby-Brown, J. M. Small, D. P. Q. Smith, R. G. Smith, W. E. D. Smyth, E. M. E. I. Sondervorst, M. A. Sorefan, W. B. Sparks, H. W. Stanley, J. Stephenson, E. A. Stevens, G. C. Swain, J. L. Swift, Nancy I. Swift, J. L. Tester, R. L. Thambugala, N. S. Thomas, S. E. Thomas, Frances M. Thornton, J. A. R. Tibbles, D. R. Tivy, D. Tree, J. H. Vance, D. J. C. Walker, D. Wallace, A. Walton, C. J. Wardle, B. L. Warner, J. P. Waterhouse, Monica E. Watkins, Sheila M. Watkinson, Janet F. Waugh, G. D. Weeden, A. G. Wells, P. A. M. Weston, T. E. T. Weston, W. J. White, C.-J. G. Wiernik, J. L. Wilkins, W. Williams, H. Wilson, Sylvia Woodbridge, J. Woodford, Sheila M. Worlledge, A. N. H. Wright, B. J. Wright, G. E. P. Wright.

[1]With honours. [2]Distinguished in pathology. [3]Distinguished in medicine. [4]Distinguished in applied pharmacology and therapeutics. [5]Distinguished in surgery. [6]Distinguished in obstetrics and gynaecology.

UNIVERSITY OF BIRMINGHAM

Dr. M. J. D. Noble has been appointed Lecturer and First Assistant in Obstetrics and Gynaecology from November 1; Dr. J. M. French, Lecturer in Pharmacology from October 1; and Dr. R. Lannigan, Robert Leith Fellow in Pathology from October 1.

Dr. C. F. Hawkins has been appointed a University Clinical Lecturer in Medicine and Mr. J. A. C. Edwards a University Clinical Lecturer in Surgery, both from April 1.

Sir James Spence has accepted an invitation to be Ingleby Lecturer for 1952.

Dr. Ernest Bulmer resigned from the post of Lecturer in Medicine on June 30. He continues as University Clinical Lecturer in Medicine.

Dr. J. McGarrity resigned from the post of Lecturer in Infectious Diseases on June 30. He also resigned his clinical lectureship.

Mr. H. H. Sampson has retired from his appointments at the United Birmingham Hospitals and from his University Clinical Lectureship in Surgery. The Board of the Faculty of Medicine has placed on record an appreciation of his services to the medical school.

UNIVERSITY OF LEEDS

Professor A. M. Claye has been appointed to the full-time Chair of Obstetrics and Gynaecology in the University from April 1, 1952. He joined the staff of the University in 1926 as Tutor in Obstetrics, and since 1929 he has been honorary obstetric surgeon to the Leeds Maternity Hospital and honorary surgeon to the Hospital for Women at Leeds. On the retirement of Professor Carlton Oldfield from the part-time Chair of Obstetrics and Gynaecology in 1930 two part-time Chairs were instituted, Professor Claye being appointed part-time Professor of Obstetrics and Professor William Gough to the Chair of Gynaecology and Head of the Department of Obstetrics and Gynaecology. When Professor Gough retired in 1936 the former arrangement of having one Chair in the combined subjects was reverted to and Professor Claye has held the part-time Chair since then.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College, held on November 6, with the President, Sir David K. Henderson, in the chair, the following were elected Fellows of the College: B. B. Morgan, John Ritchie, K. V. Krishnan, P. K. Ghosh, H. N. Robson, G. B. R. Warnock.

The following were elected Members of the College: A. T. Doig, L. Sefton, M. C. Clarke, G. S. Mahapatra, R. S. Kennedy, S. K. Nandy, Sheila Martin, A. R. R. Cumming, M. J. Purdy, L. Sagorin, S. K. N. Sinha, M. L. Sehgal, C. D. Gettliffe, A. Lyell, J. McK. Sutherland, D. A. Edington, O. M. Attia, R. S. Gupta, N. G. Guha, W. M. Fyfe, A. C. Kennedy, B. N. Lulla, V. J. Kinariwala, J. M. Macdonald, R. J. M. Coates, P. N. Behl, Leila Nair, A. C. McDougall, J. Butler, J. Newall, G. J. Sutin, B. I. Hirschowitz, J. O. Mabayoje, A. H. Siddiqui, J. E. Murray.

ROYAL COLLEGE OF SURGEONS IN IRELAND

The Fellowship of the College has been conferred on J. P. Flanagan, T. H. F. Gillespie, W. A. L. MacGowan, D. T. Ll. Nash, T. T. Swan.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a recent meeting of the Council of the Royal College of Obstetricians and Gynaecologists held in the College House, A. P. Barry was admitted to the Fellowship of the College.

The following candidates were admitted to the Membership of the College: T. L. Adamson, G. W. E. Aitken, G. J. Amiel, D. L. Arnold, K. Baker, J. S. Barr, E. L. G. Beavis, R. McF. Bernard, R. Brown, T. W. Capell, Helen A. Cawson, F. Daubenton, C. H. De Boer, Mary R. Ellis, J. M. Farrar, J. Gardiner, J. F. C. Grant, R. G. H. Hall, A. L. Hellestrand, S. R. Hewitt, D. H. McGrath, D. MacVicar, K. A. Makos, R. T. Martin, J. K. Morrison, J. K. Ogden, H. Roberts, Heather J. S. Ross, G. El D. M. K. Sami, J. C. W. Somerville, N. G. G. Talbot, J. M. Thomas, R. R. Trussell, A. C. H. Wensley, Marion Williams, L. Willoughby, Abd E. El S. A. Zikry.

The following candidates have been awarded the Diploma in Obstetrics: R. M. Aitken, E. A. Andrade, Audrey K. Arnold, Winifred A. Bailey, Jean M. Bainbridge, Anne R. Barlow, W. H. B. Begg, J. F. P. Bell, R. G. Benson, J. P. Birkett, H. J. Bland, A. M. O. Blood, R. H. Bolton, Helen K. Borg, P. H. Bright, G. W. Burton, P. L. Candler, M. I. Cassimjee, H. E. R. Chew, Ruth E. Chivers, K. R. J. Coates, Kathleen M. Cosgrove, Frances M. Cottam, J. H. Coulson, H. A. Courtney, K. McL. Crocker, R. D. Cundall, J. I. Currie, R. J. Davis, R. E. ff. Devitt, T. W. G. Donohoe, D. M. Downing, Audrey E. Draycott, R. V. Dugdale, B. H. Du Heaume, R. Eminyan, H. C. Endbinder, J. W. G. Evans, J. N Gale, W. K. Galuszka, J. A. Goldsmith, F. R. Goodwin, H. Gough-Thomas, E. H. Griffiths, Kathleen M. C. Haigh, R. D. Haigh, G. E. Haward, P. M. Healy, Mary Helmer, H. R. Hewitt, B. M. Hibbard, D. D. Hilton, Mary Hobson, Betty E. Hodgkinson, C. T. Hough, S. El-D. H. Issa, C. A. Jewels, Elizabeth M. Johnson, T. G. Jones, Sarah N. Joseph, M. S. Kay, D Keith, Brigid P. Kelly, N. Kennedy, I. H. Kidd, Dorothy I. Klein, Ellen M. Knight, D. M. Kochan, P. F. R. Lankester, K. B. Layton, S. Lourdenadin, Doreen S. Lowson, W. R. Macewan, A. Macfarlane, D. M. Mackay, K. M. McNicol, Helen M. Mair, J. G. Mann, J. F. Mark, Gillian R. S. Marshall, J. P. Martin, A. G. Mathew, J. W. B. Matthews, P. Mellor, E. D. Morris, J. B. Morris, Irene R. B. Muir, F. Mulrine, Jean Musgrave, Marian F. Natkanski, B. Needham, G. W. B. Peel, Agnes C. D. Penman, J. N. Redfern, Gwyneth Richards, G. S. Rockwood, J. S. T. Searle, M. W. Sharp, B. R. Simpson, R. I. L. Smallwood, F. H. N. Smith, Margaret W. H. Smith, D. W. Smyth, H. Spira, Pauline R. Sullivan, J. H. Swindell, J. B. Taylor, R. MacN. Thomson, M. Tua, J. K. Tully, J. A. Verzin, J. N. Ward, A. T. Watson, Jean M. I. Watson, Mary B. Watson, R. G. Watson, W. F. Watson, G. B. Whitaker, Molly T. Williams, W. J. W. Wolfe.

CONJOINT BOARD IN SCOTLAND

The following candidates, having passed the final examinations, have been granted the diploma of L.R.C.P.Ed., L.R.C.S.Ed., L.R.F.P.S.Glas.: T. Brennan, H. W. Dunnan, Nora L. Earland, J. L. Eaton, R. Fallows, T. L. Fleming, J. S. W. Frew, J. Griffin, C. S. Hajikakou, I. Hamilton, G. Irvine, D. F. Kerr, D. H. Lock, J J. McCavana, H. G. McConalogue, W. K. M. Muir, J. G. Murty, I. F. T. Norgate, R. A. A. Quarshie, R. C. Shah, S. Whitby, A. S. M. Wilson.

The Services

The *London Gazette* has announced the award of the George Medal to Surgeon Lieutenant JAMES GOLDING HARDING SHEPPARD, M.B., B.S., R.N., and Acting Leading Sick Berth Attendant (Local) MALCOLM HUGHES. The citation reads as follows:

On April 27, 1951, a lighter was being loaded with ammunition from the Naval Auxiliary vessel *Bedenham*, in His Majesty's Dockyard, Gibraltar, when a minor explosion occurred in the lighter, followed by an intense ammunition fire. Six minutes later a second large explosion occurred in the lighter which cut the *Bedenham* in two and sank her. Immediately after the first explosion, Surgeon Lieutenant SHEPPARD went to the wharf where the *Bedenham* was lying and searched for casualties. He helped to pull out of the water a badly burned man and took him to an ambulance. He was walking back towards the *Bedenham* to his first-aid box and was only about fifteen yards away when the second explosion occurred. He fortunately escaped unharmed and immediately began to administer first aid to the seriously injured on the wharf. Later, he treated other casualties in the Dockyard surgery. Surgeon-Lieutenant SHEPPARD showed a total disregard for his own safety, and his single-minded determination to do all within his power to seek out the casualties, care for them, and relieve their pain was worthy of the highest praise. Leading Sick Berth Attendant HUGHES accompanied Surgeon Lieutenant SHEPPARD to the wharf where the *Bedenham* was lying, and assisted him in the care of a badly burned man in the immediate vicinity of the burning lighter in which ammunition was exploding. He was within twenty or thirty yards of the *Bedenham* when the large explosion occurred, but was fortunate enough to escape with slight shock and minor bruises. He at once resumed his assistance with the treatment and removal of the casualties on the wharf, and then returned to the Dockyard surgery to assist there with the treatment of the injured. The coolness, courage, and devotion to duty shown by Leading Sick Berth Attendant HUGHES in the face of extreme danger was outstanding.

The *London Gazette* has announced that the notification regarding the award of the Royal Naval Reserve decoration to Surgeon Commander M. J. L. Stening, R.A.N.R. (*Journal*, September 15, p. 683), should have read Royal Naval Volunteer Reserve decoration.

A *Supplement* to the *London Gazette* has announced the following awards:

Fourth Clasp to the Territorial Efficiency Decoration.—Colonel (Honorary Brigadier) F. R. Sandford, C.B.E., M.C., T.D., K.H.P., and Major (Honorary Colonel) W. R. Martine, O.B.E., T.D., R.A.M.C.

First and Second Clasps to the Territorial Efficiency Decoration.—Lieutenant-Colonel T. C. Williams, T.D., Major (Acting Colonel) W. M. Evans, O.B.E., M.C., T.D. (now Supplementary Reserve), Majors (Honorary Lieutenant-Colonels) A. McC. Campbell, D.S.O., O.B.E., T.D., and E. A. L. Murphy, T.D., and Major P. Brookes, T.D., R.A.M.C.

Territorial Efficiency Decoration.—War Substantive Major C. E. Sykes and Captain E. Fulford (retired), R.A.M.C.

Dr. David Ross has been named medical director of the National Hospital for Speech Disorders, New York City, in succession to the late Dr. James S. Greene, who founded the hospital in 1916 with two helpers and served as its head until his death in 1950. After graduating from Glasgow University, Dr. Ross trained in psychiatry at the Maudsley Hospital, the Cassel Hospital, and elsewhere. The National Hospital for Speech Disorders is the only medical institution in the world devoted exclusively to the diagnosis and treatment of speech and voice disorders. Since being opened in November, 1916, it has treated over 78,000 speech sufferers, approximately 63% of them without charge. Attending the institution during the past year have been speech sufferers from Canada, South America, Israel, China, and New Zealand. One entire floor of the hospital is devoted to the treatment of pre-school and kindergarten children. Another department, for men and women who have undergone operations for removal of the larynx because of cancer, is devoted to teaching these larynxless patients to speak again.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending November 10 (No. 45) and corresponding week 1950.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 126 great towns in England and Wales (London included), London administrative county, the 16 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 13 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1951					1950				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	42	2	14	0	0	55	1	15	2	4
Dysentery	192	28	63	1	1	411	61	146	6	
Encephalitis, acute	6	0	1	0	1	3	0	0	0	
Enteric fever:										
Typhoid	4	2	0	0	0	3	1	1	0	0
Paratyphoid	10	0	0	1		3	0	1 (B)	0	
Food-poisoning	95	13		3		144	28		1	
Infective enteritis or diarrhoea under 2 years				24	18				20	42
Measles*	1,935	50	90	131	124	8,857	544	195	120	100
Meningococcal infection	37	3	9	4	1	26	3	11	1	2
Ophthalmia neonatorum	32	2	7	0		26	4	13	0	
Pneumonia†	479	34	199	8		465	20	148	16	
Poliomyelitis, acute:										
Paralytic	56	5	10	2	2	225	11	22	4	1
Non-paralytic	22	4								
Puerperal fever§	220	27	19	0	1	82	6	13	1	1
Scarlet fever	1,232	122	302	26	55	1,206	99	199	55	104
Tuberculosis:										
Respiratory			130	29				158	36	
Non-respiratory			37	4				22	5	
Whooping-cough	1,625	61	353	45	82	3,725	285	454	36	64

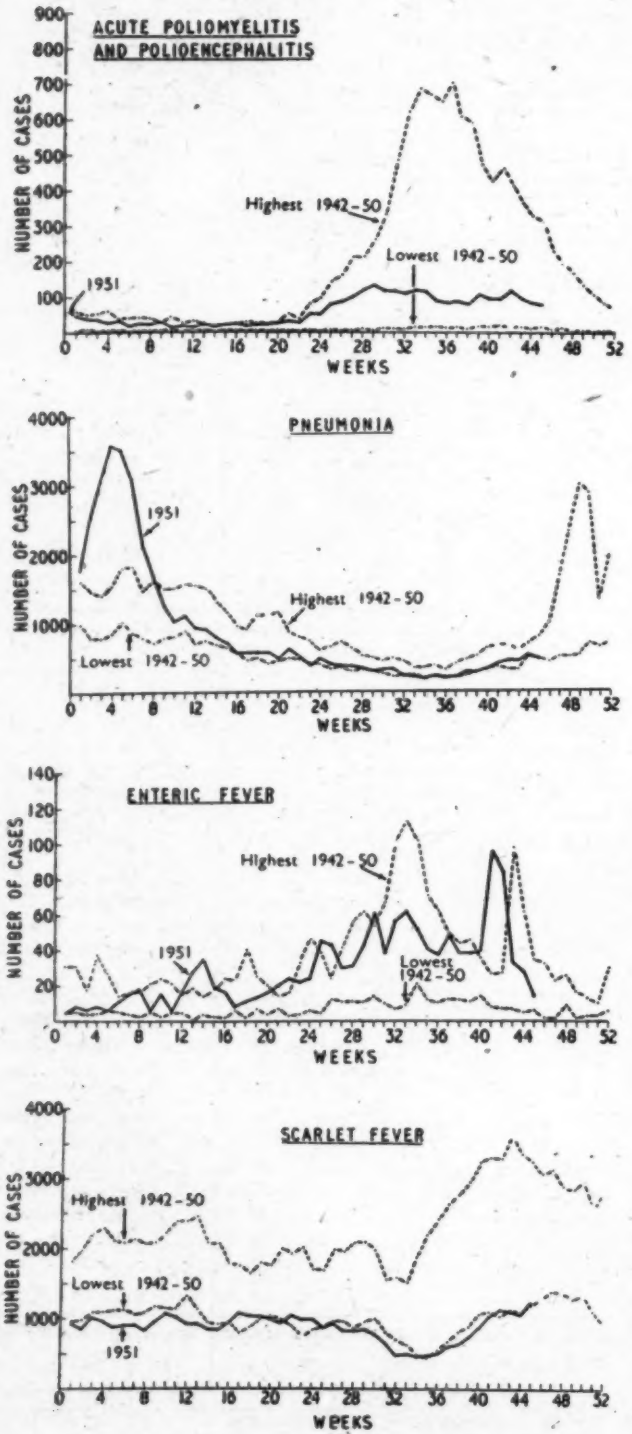
DEATHS in Great Towns	1951					1950				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	0	0	0	0	0	0
Dysentery		0		0			0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8		3	0	2	17		3	1	1
Influenza	22	5	0	0	0	20	3	3	0	1
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		2	0				1	0		
Pneumonia	195	39		8	6	177	23		13	5
Poliomyelitis, acute	3	0			0	9	1			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	124	20	19	9	12	171	25	32	6	7
Non-respiratory		1	3	0	2		2	3	3	0
Whooping-cough	1	0	1	0	0	2	1	1	0	0
Deaths 0–1 year	206	23	28	2	13	224	30	34	12	13
Deaths (excluding stillbirths)	4,891	762	572	98	147	5,101	814	635	129	181
LIVE BIRTHS	5,973	971	671	185	407	6,441	1036	768	174	381
STILLBIRTHS	154	16	22			159	26	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus -------, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



Infectious Diseases

In England and Wales during the week ending November 10 notifications of scarlet fever increased by 165 and whooping-cough by 148, while those for measles decreased by 58.

The number of scarlet fever notifications was the highest for almost a year. The rise in incidence during the past two months has been larger in the south of the country than in the north. During the week reviewed the largest local increase in scarlet fever was 54 cases in Lancashire. There were small rises in the numbers of notifications of whooping-cough in many areas, the largest being Lancashire 35 and Southampton 33. The notifications of diphtheria were 4 fewer than in the preceding week. The chief feature of the returns of diphtheria was a decrease of 3 in London. The largest regional decrease in the number of notifications of measles was 82 in Wales. The counties with the largest falls in the incidence of measles were Kent 52 and Warwickshire 43, and the largest rises were Yorkshire West Riding 48 and Staffordshire 39.

The notifications of paratyphoid fever were 16 fewer than in the previous week; 4 of the 10 cases recorded during the week were notified from Lancashire, Whiston R.D.

The number of notifications of paralytic acute poliomyelitis were 6 fewer and the non-paralytic 2 more than in the preceding week. The largest returns were Yorkshire West Riding 17 (Sheffield C.B. 6), Lancashire 12, London 9 (4 more than in the previous week).

There were 17 more cases of dysentery than in the preceding week. Two new outbreaks, each with 10 notifications, were reported: they were Hereford, Leominster and Wigmore R.D., and Derbyshire, Repton R.D. The largest returns were Lancashire 41 (Bootle C.B. 14, Lancaster M.B. 8), London 28, Middlesex 19, Surrey 13, Warwickshire 11 (Birmingham C.B. 8).

Week Ending November 17

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,473, whooping-cough 1,833, diphtheria 38, measles 2,084, acute pneumonia 467, acute poliomyelitis 65, dysentery 240, paratyphoid fever 14, and typhoid fever 4.

Medical News

"Any Questions?"

Early this month, in good time for Christmas, the first book of "*Any Questions?*" will be published. The book contains a selection of the best questions and answers which have appeared in the "Any Questions?" section of the *Journal* since the feature was started eight years ago. Many of these authoritative answers give practical information not yet in the textbooks. This book is confidently recommended to all practitioners. "*Any Questions?*" is strongly bound in cloth, small enough to fit the pocket, and costs 7s. 6d. (postage 6d.). Copies may be obtained on application to the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

A Book for Christmas

50 Years of Medicine, containing in book form articles surveying the progress of medicine and surgery during the first half of this century which appeared in a special number of the *Journal* last year, is again available. Very pleasantly brought out, and handsomely bound, not only does it look impressive but the information it gathers together is useful and enlightening, and is of interest to both lay and medical readers. Over 300 pages of text, a complete index, and 32 illustrations make this a valuable book to have, and, incidentally, an excellent Christmas present. Costing 15s., *50 Years of Medicine* may be obtained through booksellers, or direct (post free) from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Radiologists Warned

The attention of all radiologists who are intending to apply for appointments in Canada is drawn to the importance of communicating with the honorary secretary of the Royal College of Physicians and Surgeons of Canada, 150, Metcalfe Street, Ottawa, so that they will be fully aware of their position concerning certification examinations, as preferment and promotion are largely dependent on such certification.

Hood Medal for Institute of Ophthalmology

Each year the Royal Photographic Society gives a medal for the most meritorious exhibit in any branch of practical photography offered to its annual exhibition. This year it has gone to the Medical Illustration Department of the Institute of Ophthalmology, London, which is under the direction of Dr. Peter Hansell—the first time the medal has been awarded for applied medical photography, and also the first time it has been presented to a unit and not an individual.

Annual Dinner of the Society of Medical Officers of Health

The annual dinner was held at the Piccadilly Hotel on November 22. It was appropriate that the speeches had a distinctly Scottish flavour, since the President of the Society is Dr. W. G. Clark, the first M.O.H. of Edinburgh to hold that office. The main toast of the evening was proposed by Miss P. Hornsby Smith (Parliamentary Secretary, Ministry of Health), who paid tribute to the preventive medical services and affirmed that recent events had not in any way minimized their value. Social hygiene was still a field of limitless possibilities. In reply, Dr. Clark said that the politicians had managed to divide the doctors into four groups. "As we look at them, can we believe that any of them are happy?" The general practitioners were troubled about the capitation fee, the medical officers of health about the Industrial Court award, the consultants about the merit awards, and the medical Civil Servants about the recommendations of the Howitt Committee. The Service would never be efficient unless it was a happy one: there should be no antagonism between the various branches of the profession and all should work together for the common weal. If local authorities were given freedom, as in the past, to try out social remedies, Dr. Clark thought that peptic ulcers and many circulatory disorders might eventually disappear. Sir Allen Daley proposed the health of the guests, and responses were made by Commander T. D. Galbraith (Under Secretary of State for Scotland), Sir Andrew Davidson (Chief Medical Officer, Department of Health for Scotland), and Mr. Homer N. Calver, of the American Public Health Association.

N.A.P.T. Luncheon to Sir Robert Young

The members of the council of the National Association for the Prevention of Tuberculosis gave a private luncheon on November 15 at the Connaught Rooms to Sir Robert A. Young, the vice-chairman, in celebration of his 80th birthday. The Duchess of Portland presided at the luncheon, and, on behalf of the Council, presented Sir Robert with a gift of books.

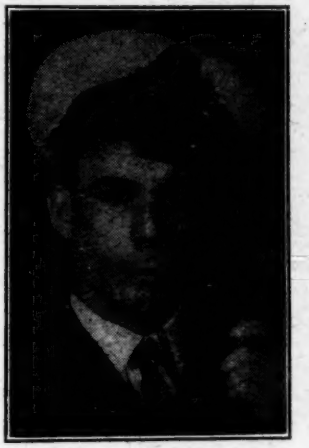
Central Council for Health Education

Dr. John Burton has been appointed Medical Director of the Central Council for Health Education and editor of the *Health Education Journal*. He was formerly deputy medical adviser to the Council. The Central Council for Health Education is the agency to which local authorities in England, Wales, and Northern Ireland look for guidance in carrying out their health education work, and is supported by voluntary contributions.

West Midlands Physicians Association

The third meeting was held at the Queen Elizabeth Hospital, Birmingham, on November 17, when Professor T. L. Hardy was elected president in succession to Dr. Bruce Maclean.

George Medal for Surgeon Lieutenant



On April 27 this year a lighter was being loaded with ammunition from the naval auxiliary vessel *Bedenham* at Gibraltar, when an explosion occurred and fire followed. Surgeon Lieutenant James G. H. Sheppard searched for casualties, and in spite of a second explosion only 15 yards away continued to treat them, with a total disregard for his own safety. He has now been awarded the George Medal. He was educated at Beaumont College and St. Bartholomew's Hospital, qualifying M.B., B.S. in 1948. After a time as resident medical officer at the General Hospital, Jersey (C.I.), he volunteered for the Navy. He was married last July, his wife being a physiotherapist at Guy's Hospital. (See full citation on p. 1353.)

Brompton Hospital Association

About 130 medical men and women connected in one way or another with the Brompton Hospital and its sanatorium at Frimley dined together on November 23 with their president, Sir Robert Young, in the chair. The toast of the Brompton Hospital Association was proposed in a witty speech by Sir Geoffrey Todd, and then Dr. F. H. Young toasted "our first president." This afforded another occasion for congratulating Sir Robert on his 80th birthday, and in his charming and witty speech of reply he showed once more how lightly his 80 years sit on his shoulders. The Brompton Hospital Association was formed recently with the idea of providing an opportunity for former residents and others to meet and foster friendships formed at the hospital and the sanatorium. The idea at present is that the "B.H.A." should hold a dinner about once in two years. But the success of the dinner last week may encourage those who organize these occasions to enable the members of the "B.H.A." to get together perhaps more frequently. Anyone who does not know of this association should write for information to the Honorary Secretary, The Brompton Hospital Association, Brompton Hospital, London, S.W.3.

Frank Thomas Paul (1851–1941)

Frank Thomas Paul, who was born 100 years ago, on December 3, 1851, spent his entire surgical life in Liverpool, where he was for 20 years surgeon to the Royal Infirmary and, for a time, professor of medical jurisprudence and dean of the medical school. Pioneer in the surgery of the abdomen, he has acquired eponymous fame through Paul's tube and Paul's operation. His glass and rubber tubes, used after a colostomy, were first mentioned in this *Journal* in 1891 (**2**, 118), while his operation of extra-abdominal resection of the colon was lucidly described in 1895 (**1**, 1136). His paper apparently was not read abroad, for three years later von Mikulicz-Radecki advocated a similar method of resection, which likewise included crushing of the spur. The operation is known to-day as the Paul–Mikulicz operation. Paul was one of the most brilliant and exquisite operators in recent times, and a most modest, self-effacing man of wide interests. He died on January 17, 1941, in his ninetieth year.

Emergency Bed Service: Applications and Admissions

During the seven days ending November 26 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 838, of whom 90.81% were admitted.

COMING EVENTS

Contraceptive Technique

A lecture and demonstration (on living models) on contraceptive technique will be given by Marie C. Stopes at the Mothers' Clinic, 108, Whitfield Street, London, W.1, on Thursday, December 6, at 2.30 p.m. Tickets must be obtained in advance, as space is limited.

Osler Club

At a meeting to be held at the Medical Society of London, 11, Chandos Street, Cavendish Square, W.1, on Friday, December 7, at 7.45 p.m., Dr. R. G. W. Ollerenshaw will speak on the history of medical illustrations, and Mr. R. B. Fishenden, Editor of the *Penrose Annual*, and Technical Editor of King Penguin books, will deal with modern methods of book illustration. Both talks will be illustrated. Professor James Whillis and Dr. Peter Hansell, Editor of *Medical and Biological Illustration*, will speak in the discussion. Visitors will be welcomed.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, E.C., December 3, 7 for 7.30 p.m., dinner-meeting; "*Insomnia*," discussion to be opened by Professor A. St. J. Huggett, Dr. John Hunt, and Dr. G. W. B. James.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—December 3, 5.30 p.m., lecture-demonstration for postgraduates by Dr. E. Stengel.

OXFORD UNIVERSITY.—At Physiology and Biochemistry Lecture Room, Oxford, December 3, 12 noon, "*Dietary Effects on Human Performance*," by Professor Ancel Keys (University of Minnesota).

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN, 17, Bloomsbury Square, London, W.C.—December 3, 7.30 p.m., "*The International Pharmacopoeia*," by Dr. C. H. Hampshire.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—December 3, 4 p.m., "*Coronary Thrombosis and Its Treatment*," by Dr. Rae Gilchrist.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—December 3, 3.45 p.m., "*The Knee-joint*," Arnott Demonstration by Professor R. J. Last.

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 3, 3.30 p.m., "*Pain*," by Sir Daniel Davies; 5 p.m., "*Anti-coagulant Therapy*," by Dr. Arthur Willcox.

UNIVERSITY COLLEGE: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, London, W.C., December 3, 5.15 p.m., "*Acetylcholine and the Central Nervous System*," Public Lecture by Dr. W. S. Feldberg.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., December 4, 5.30 p.m., "*The Rate and Materials of Blood Formation*," by Professor L. J. Witts.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 4, 5.30 p.m., "*Bullous Eruptions*," by Dr. H. J. Wallace.

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—December 4, 5 p.m., "*The History of Certain Therapeutic Procedures*," FitzPatrick Lecture by Dr. William Brockbank.

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 4, 3.30 p.m., "*Physical Medicine*," by Dr. W. S. Tegner; 5 p.m., "*Glandular Dystrophies*," by Dr. H. Gardiner-Hill.

SOCIETY OF CHEMICAL INDUSTRY: MICROBIOLOGY GROUP.—At Medical Society of London, 11, Chandos Street, Cavendish Square, W., December 4, 6.15 p.m., "*Industrial Microbial Enzymes*," by Dr. M. Horwood.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—December 4, 5.30 p.m., "*Head Injury*," clinical demonstration by Mr. G. C. Knight.

Wednesday

●DAVIDSON CLINIC, 58, Dalkeith Road, Edinburgh.—December 5, 8 p.m., "*Opposition to Psychology*," by Dr. A. J. Bain.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 5, 5.30 p.m., "*X-ray Technique*," by Dr. C. W. McKenny.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., December 5, 4.30 p.m., "*Diminished Fertility in the Male*," by Mr. A. R. C. Higham.

●LONDON MARRIAGE GUIDANCE COUNCIL, 78, Duke Street, Grosvenor Square, W.—December 5, 6 p.m., "*The Medical Aspects of Marriage Preparation*," by Dr. Philip M. Bloom.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—December 5, 11.45 a.m., medical clinical-pathological conference.

●ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, London, S.W.—December 5, 5 p.m., "*Disorders of the Adrenal Cortex*," by Dr. P. M. F. Bishop.

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 5, 3.30 p.m. and 5 p.m., "*A Review of Antibiotics*," by Dr. E. R. Cullinan.

SOCIETY OF PUBLIC ANALYSTS.—Joint meeting with Food Group of Society of Chemical Industry, at Chemical Society, Burlington House, Piccadilly, London, W., December 5, 7 p.m., "*The Food Standards Issue—What Does the Future Hold?*" Contributions by Mr. T. McLachlan and Mr. C. L. Heller. Discussion.

Thursday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., December 6, 5.30 p.m., "*Alimentary Factors in Blood Formation*," by Professor L. J. Witts.

EPSOM AND SUTTON INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At Belmont Hospital, Sutton, December 6, 8 p.m., "*The Scope of Shock Treatment in the Neuroses*," by Dr. D. Shaw; "*Ether, Methedrine, and CO_2 in the Neuroses*," with practical demonstrations, by Dr. William Sargant; "*Socio-therapy Techniques*," by Dr. Maxwell S. Jones. Discussion after each paper.

FACULTY OF HOMOEOPATHY, Royal London Homoeopathic Hospital, Great Ormond Street, London, W.C.—December 6, 5 p.m., "*Some Personal Ideas about the Modern Homoeopathic Treatment of Acute, also Tropical Infections*," by Dr. C. L. W. Overman (Breda, Holland).

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, December 6, 5 p.m., "*The Hazards of Major Surgery*," by Mr. John Bruce.

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—December 6, 5 p.m., "*Common Feeding Difficulties*," by Dr. R. MacKeith.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 6, 5.30 p.m., "*Cyto-diagnosis in Dermatology*," by Dr. H. Haber.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—December 6, 3 p.m., "*The Anatomy of Learning*," by Professor J. Z. Young.

LONDON COUNTY MEDICAL SOCIETY.—At Central Histological Laboratory, Whitting Hospital, Archway Road, N., December 6, 3 p.m., clinical meeting.

MEDICAL ART SOCIETY.—At 11, Chandos Street, London, W., December 6, 8 p.m., "*The Trend of Modern Art*," by Mr. Paul Smythe. He will afterwards criticize members' work.

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—December 6, 5 p.m., "*Counter-irritation Intravenous Injection of Drugs*," FitzPatrick Lecture by Dr. William Brockbank.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—December 6, 5.30 p.m., "*Simple Tumours and Hyperostoses of the Upper Jaw*," Otolaryngology Lecture by Mr. S. H. Wass.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, December 6, 5 p.m., "*The Diagnosis and Treatment of Hypopituitarism*," by Professor H. L. Sheehan.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—December 6, 4.30 p.m., lecture-demonstration in psychiatry by Sir Paul Mallinson.

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 6, 3.30 p.m., "*The Use and Abuse of Drugs*," by Dr. H. Davis, Ph.D., F.R.I.C.; 5 p.m., "*The Use and Abuse of Drugs*," by Dr. C. A. Keele.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—December 6, 5.30 p.m., "*Some Unsolved Problems of Biology*," by Professor P. B. Medawar, F.R.S. Inaugural lecture.

Friday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—December 7, 5.30 p.m., "*Bullous Eruptions*," clinical demonstration by Dr. H. J. Wallace.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—December 7, 5 p.m., "*Physiology of the Vestibular Apparatus*," by Professor D. Slome.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Hammersmith Hospital, Ducane Road, W.—December 7, 11.15 a.m., surgical clinical-pathological conference; 2 p.m., "*Various Methods of Arthrodesis*," by Mr. H. A. Brittain; 4 p.m., "*Haemodynamics of Peripheral Vascular Disease*," by Professor E. P. Sharpey-Schafer.

●ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, London, S.W.—December 7, 5 p.m., *"Non-tuberculous 'Miliary' Lung Lesions,"* by Dr. J. G. Scadding.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 7, 5 p.m., *"Recent Applications of Physiology and Pharmacology to Ocular Therapeutics,"* by Miss M. Savory.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—December 7, 8 p.m., brains trust.

SOCIETY OF APOTHECARIES OF LONDON, Black Friars Lane, Queen Victoria Street, E.C.—December 7, 3.30 p.m., *"Burns and Blast,"* by Sir Cecil Wakeley, P.R.C.S.; 5 p.m., *"Suppurative Pneumonia,"* by Dr. Howard Nicholson.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, London, E.—December 7, 8 p.m., *"Hypnotism—Its Uses and Limitations in Medicine,"* by Dr. Henry Yellowlees.

Saturday

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, Royal National Throat, Nose, and Ear Hospital, Gray's Inn Road, London, W.C.—December 8, 11.30 a.m., *"Some Remarks on the Function of the Vestibular Organ,"* by Professor L. B. W. Jongkees (Amsterdam).

APPOINTMENTS

LIVERPOOL REGIONAL HOSPITAL BOARD.—*Whole-time Consultant Pathologist to Hospitals in Southport Hospital Management Committee Group,* J. G. Benstead, M.D. *Whole-time Assistant Pathologist to Liverpool Radium Institute,* Edith M. McConnell, M.D. *Whole-time Medical Director of No. 2 Mobile Mass Radiography Unit,* P. Keaney, M.B., B.Ch.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Consultant Psychiatrist to Bristol Mental Hospitals,* Stanley Smith, M.D., M.R.C.P., D.P.M. *Senior Hospital Medical Officer Psychiatrist to Bristol Mental Hospitals,* E. H. Hare, M.D., D.P.M. *Assistant Anaesthetist to South Somerset Clinical Area,* T. Llewelyn Jones, M.B., B.Ch. *Assistant Psychiatrist to St. Lawrence's Hospital, Bodmin,* E. E. Feldmesser, M.D. *Medical Superintendent, Mendip Hospital, Wells,* W. E. W. Bridger, M.D., D.P.M.

TAYLOR, ELLIS, M.B., Ch.B., D.P.H., Divisional Medical Officer, Lancashire County Council (Health Division No. 14); Medical Officer of Health, Borough of Middleton and Urban District Councils of Chadderton, Crompton, Failsworth, Lees, and Royton.

WOOLGROVE, CYRIL GEORGE, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health and School Medical Officer, County Borough of Reading.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bailey.—On November 5, 1951, at Queen Elizabeth Hospital, Birmingham, to Dr. Catherine Gilray Bailey (formerly Simpson), wife of John Oswald Bailey, 72, Russell Road, Moseley, Birmingham, a son.

Davis.—On November 19, 1951, in London, to Dr. Renate Marie Davis (formerly Loeser), wife of Albert Davis, F.R.C.S., a son.

Duff.—On November 18, 1951, to Audrey (formerly Heaton-Smith), wife of Dr. A. Dewar Duff, 5, Tanza Road, London, N.W., a son—John Dallas.

Kader.—On November 24, 1951, at Warneford General Hospital, Leamington Spa, to Pauline, wife of Captain Leonard Kader, R.A.M.C., a son—Paul Richard Cheney.

Normandale.—On October 24, 1951, at the British Military Hospital, Klagenfurt, Austria, to Mary, wife of Captain Peter Normandale, R.A.M.C., a son—Rory.

Pippard.—On November 18, 1951, at The London Hospital, to Kathleen, wife of Dr. John Pippard, a third son—David Alan.

Primrose.—On November 18, 1951, at Brora, Sutherland, to Mrs. Primrose, wife of Dr. E. J. R. Primrose, a daughter.

Watson.—On November 20, 1951, at Harrogate General Hospital, to Margaret Sarah (Peggie) (formerly Lowis), wife of Dr. J. E. Watson, 6, St. Roberts Road, Knaresborough, Yorkshire, a second son.

MARRIAGE

Ostlere—Patten.—On November 24, 1951, at Mansfield College Chapel, Oxford, Gordon Stanley Ostlere, M.B., B.Chir., D.A., to May Patten, M.B., Ch.B., M.R.C.P.Ed., D.A.

DEATHS

Bletchly.—On November 2, 1951, George Playne Bletchly, M.R.C.S., L.R.C.P., of Nailsworth, Glos, aged 79.

Chambers.—On November 25, 1951, at her home, 370, Upper Richmond Road, Putney, London, S.W., Grace Dorothy Chambers, M.D.

Chiene.—On November 19, 1951, suddenly, at 11, Magdala Crescent, Edinburgh, George Lyall Chiene, F.R.C.S.Ed., aged 78.

Colquhoun.—On November 22, 1951, at a nursing-home, Gideon Robert Ernest Colquhoun, F.R.C.S.

Glenn.—On November 22, 1951, at Muster Green, Haywards Heath, Sussex, Cecil Hayward Glenn, M.B., B.Ch., aged 77.

Neave.—On November 17, 1951, Lionel Digby Neave, M.R.C.S., L.R.C.P., of 11, Colchester Road, St. Osyth, Essex.

Noott.—On November 20, 1951, at a Bournemouth nursing-home, Geoffrey Noott, M.R.C.S., L.R.C.P., J.P., aged 66.

Preston.—On November 17, 1951, at his home, Mount Crescent, Fleetwood, Lancs, Ian Mackergow Preston, M.R.C.S., L.R.C.P., aged 49.

Young.—On November 19, 1951, in hospital, Frances Deans Young, M.B., Ch.B., of 1339, Pollokshaws Road, Glasgow, late of Nagpur, India.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

A Cry from the Womb

Q.—*Are there any authenticated records of the foetus being heard to cry out in utero? If so, what are the risks of the foetus being asphyxiated?*

A.—Crying of the foetus *in utero* is a phenomenon which is mentioned in most of the larger textbooks on obstetrics and is termed "vagitus uterinus." It was the subject of an article by I. M. Jackson in the *British Medical Journal* (1943, **2**, 266), and three further cases have since been described in our correspondence columns (1947, **2**, 508, 672, 931). G. H. Ryder (*Amer. J. Obstet. Gynec.*, 1943, **46**, 867), in recording one case, reviewed 122 others in the literature, the earliest dating back to 1546. He regarded all these as authentic, having discarded the doubtful ones.

The presence of air in the amniotic sac is essential to the occurrence of vagitus uterinus, and the membranes must therefore be ruptured. Air may enter the uterus spontaneously or during manipulations in labour or during the induction of labour by puncturing the membranes with a catheter, etc. Foetal crying has been heard both before and during labour, and Jackson says the cry is of two kinds: (1) A gentle whimpering cry due to air passing in and out of the chest with the ordinary intrauterine movements of the chest wall. This is of little importance, and the foetus usually suffers no harm. (2) A sharp gasping and louder cry which may be associated with intrauterine asphyxia. Here the foetus must be delivered quickly if it is to be saved. Vagitus uterinus is therefore not necessarily of serious import, and Ryder puts the foetal mortality at 19% in earlier cases, but only 12% in more recent ones. Nearly always, however, the foetus has been born within a few hours, or at most a few days, of the time when the cry was first heard. According to Ryder the longest recorded interval is two weeks.

Mumps and the Ovaries

Q.—*What disorders of menstruation and reproductive function may follow a mumps oophoritis? Can one estimate the amount of damage done in any way—by, for instance, hormone assays?*

A.—Oophoritis appears to be a much less common complication of mumps than is orchitis. It is difficult to be certain, however, because the symptoms and signs are less obvious. When it does occur it is not usually serious, and it is extremely rare to see permanent and significant ill effect on ovarian function follow mumps.

In its acute phase mumps oophoritis is likely to disturb the one menstrual period which follows it, either precipitating it early or postponing it, and possibly affecting the duration and amount of flow. Afterwards the cycle returns to normal. Permanent injury, if it occurs, affects the Graafian follicles, causing their destruction. If such changes affect only a few or a moderate number of follicles it does not matter, but if they are widespread throughout both ovaries they result in atrophy of the uterus and vagina, amenorrhoea or infrequent menstruation, sterility or lowered fertility, and possibly menopausal symptoms. The mechanism behind these is essentially the same as that which occurs at the normal menopause, so the likely hormonal changes are a decreased oestrogen and an increased gonadotrophin output in the urine. Unless the damage is enough to cause amenorrhoea hormone assays would not reveal any significant departure from the normal.

What the "Any Questions?" Book Contains

Q.—*What subjects are covered in the book "Any Questions?"*

A.—The first collection of *Any Questions?* in book form (obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1. Price 7s. 6d., postage 6d.) has the following chapter headings: Allergy; Anaesthesia; Blood Disorders; Cancer; Cardiovascular System; Dermatology; Ear, Nose, and Throat; Endocrinology; Fevers; Forensic Medicine and Toxicology; Gastro-intestinal Diseases; General Medicine; Gynaecology; Heredity and Disease; Immunization; Neurology; Nutrition; Obstetrics; Ophthalmology; Orthopaedics; Paediatrics; Tuberculosis; Urinary Disorders; Venereal Disease; Worms; Final Miscellany.

"Nursery Nose"

Q.—*I have been having a good deal of trouble with running noses in a residential nursery of 20 children (0 to 3 years). Can you suggest how I should deal with this problem?*

A.—This offers a problem which is perhaps insoluble to-day. Running noses and similar persistent infections are a good reason against sending children to day nurseries and residential nurseries of any size, if there is any alternative.

Good food plays a part in prevention, in that liability to infection is possibly commoner in the undernourished child. Adequate ventilation, approximating to open-air life, and frequent scrubbing out of playrooms may help; ensuring that each child has its own towel and the use of destructible handkerchiefs are of some value. Antiseptic sprays, atomizers, and irradiation with ultra-violet light are of no practical use.

The bigger the group of small children in frequent contact with each other, the more certain it is that they will develop upper respiratory infections almost continuously. In theory the first step is the limitation in number of each group of children in contact with each other. The next step is the isolation of any child and exclusion of any member of the staff who seems to be developing a cold. Unfortunately neither of these pieces of advice is often practicable. Swabbing of noses and throats of children and staff in an effort to detect carriers of offending bacteria may help, but only if it is possible to exclude any carriers who are found until they become negative. In fact, in the absence of a really well designed nursery supplied with ample staff, so that the children can be kept in small separate families, careful attention to ordinary hygienic measures is likely to be as effective as anything else.

Fertilizers and the Food Value of Crops

Q.—*Have artificial fertilizers any adverse effects on the nutritional value of food crops?*

A.—It is impossible to answer this question adequately in the space available. The use and specially the improper use of artificial fertilizers may alter the proportions of the natural constituents of food crop plants by inducing an unnatural rate of growth, but this does not necessarily mean that the nutritional value of the food is seriously disturbed.

The subject is discussed in the *Year Book of Agriculture*, 1943–7, U.S. Department of Agriculture (pp. 494–5). An example quoted is the production of excessive foliage in tomato plants so that shading of the fruit brings about a reduction in the vitamin-C content.

NOTES AND COMMENTS

Fluoride Solutions for the Teeth.—Dr. H. T. ROPER-HALL (Birmingham) writes: Your correspondent in answering this question ("Any Questions?" November 3, p. 1102) has adopted a very discouraging attitude. Research is proceeding on a large scale in Canada, New Zealand, U.S.A., and this country, with encouraging results which indicate that topical application of sodium fluoride to the teeth of suitable children has an inhibiting effect upon dental caries. L. I. Grossman ("Control of Dental Caries," p. 21 in Lippincott's *Handbook of Dental Practice*, 1948) says: "It has been shown by a number of investigators that the application of a fluoride solution to the teeth is an effective means of reducing the frequency of dental caries 10% to 40%, depending upon the number of applications, the method of application, the strength of solution used, etc." And Stones (*Oral and Dental Diseases*, 1948, p. 269) accepts these results and others, but wisely states that a complete picture of results will depend upon many years of research. Your correspondent is prejudicing the value of this research in a field which for almost the first time in large-scale dental research and treatment is *preventive* rather than curative.

OUR EXPERT writes: There was no intention of discouraging *investigation* of the effects of topical applications of fluorides to the teeth in relation to the initiation and spread of dental caries. The intention was to discourage the indiscriminate use of such remedies until their scientific value is adequately established. It is suggested that note should be taken of the findings of Stones, Lawton, Bransby, and Hartley (*Brit. dent. J.*, 1949, **86**, 263) and of others whose properly controlled tests have not substantiated the more publicized results of others.

Intestinal Myiasis.—Dr. GUSTAV ENGLER (Panama) writes: I beg to differ from the reply to the inquiry regarding intestinal myiasis caused by *Cochliomya chloropyga* ("Any Questions?" September 15, p. 688). Intestinal myiasis is a well-defined serious disease and will not yield to "proper hygienic methods." All stages of the larval period occur within the intestine. The ova lodge in the crypts of the rectum and may survive for months. Craig and Faust (*Clinical Parasitology*, 3rd ed., p. 611) list the following species as proved causes of human intestinal myiasis: *Musca domestica, Muscina stabulans, Fannia canicularis, F. scalaris, Cochliomya chloropyga, C. putoria, Calliphora vomitoria, C. erythrocephala, Aphiochaeta scalaris, Piophila casei* ("cheese skipper"), *Hermetia illucens* ("soldier fly"), *Rhypus fenestralis, Eristaloides sp.* and *Drosophila spp.* While systemic myiasis is fairly common here in Panama, *C. chloropyga* has not been observed, so far as I know. Our cochliomya infestations (*hominivorax* and *macellaria*) yield readily to irrigations with a mixture of 10% chloroform in milk. I suggest high enemas with this mixture for the case of intestinal myiasis described by your correspondent.

OUR EXPERT writes: There does not seem to be any published series of sufficiently carefully controlled clinical or experimental observations to establish beyond criticism that intestinal myiasis is in itself a serious disease that will not yield to proper hygienic measures. It would be interesting to know how the proof was obtained that ova may lodge in the crypts of the rectum and survive there for months. While it is not denied that many species of larvae have been associated with intestinal myiasis, this in itself proves no more than that such species have passed along the intestinal canal; it does not prove that they have persisted or developed for long within the gut or that they are the cause of serious organic disease.

Scalp Dressings.—Dr. D. COWAN (Johannesburg) writes: May I mention a method of securing scalp dressings ("Any Questions?" October 20, p. 986) which I have used for many years and which requires no bandages, "elastoplast," or collodion? When suturing the laceration, two or more sutures (depending on the length of the laceration) are placed *in situ* and left untied. A narrow folded length of gauze is then placed over the sutured laceration and firmly held in place by tying the ends of the open sutures. In using this method an unnecessarily large shaved area is obviated.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Alitology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.
ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*
MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the ASSOCIATION. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*
B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.